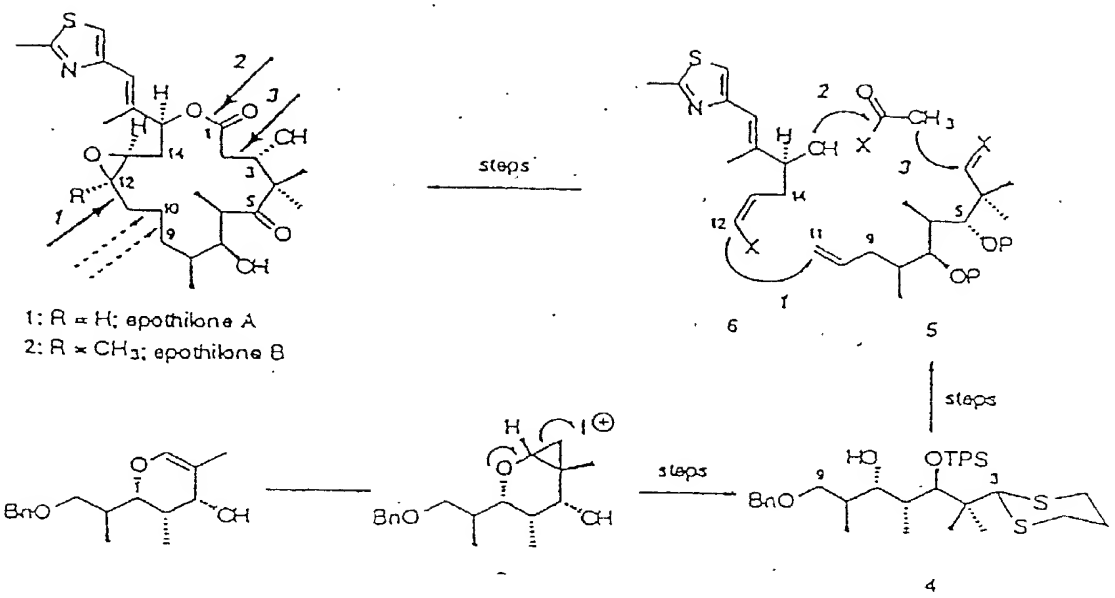
(A)



(B)

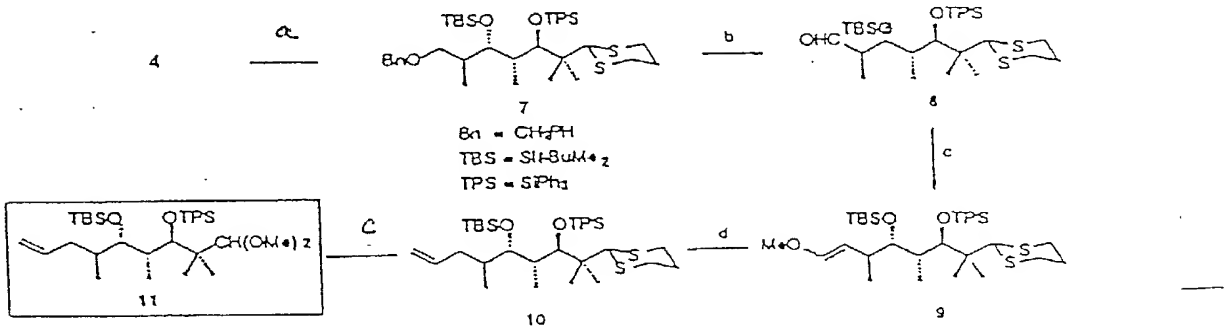


Figure 1

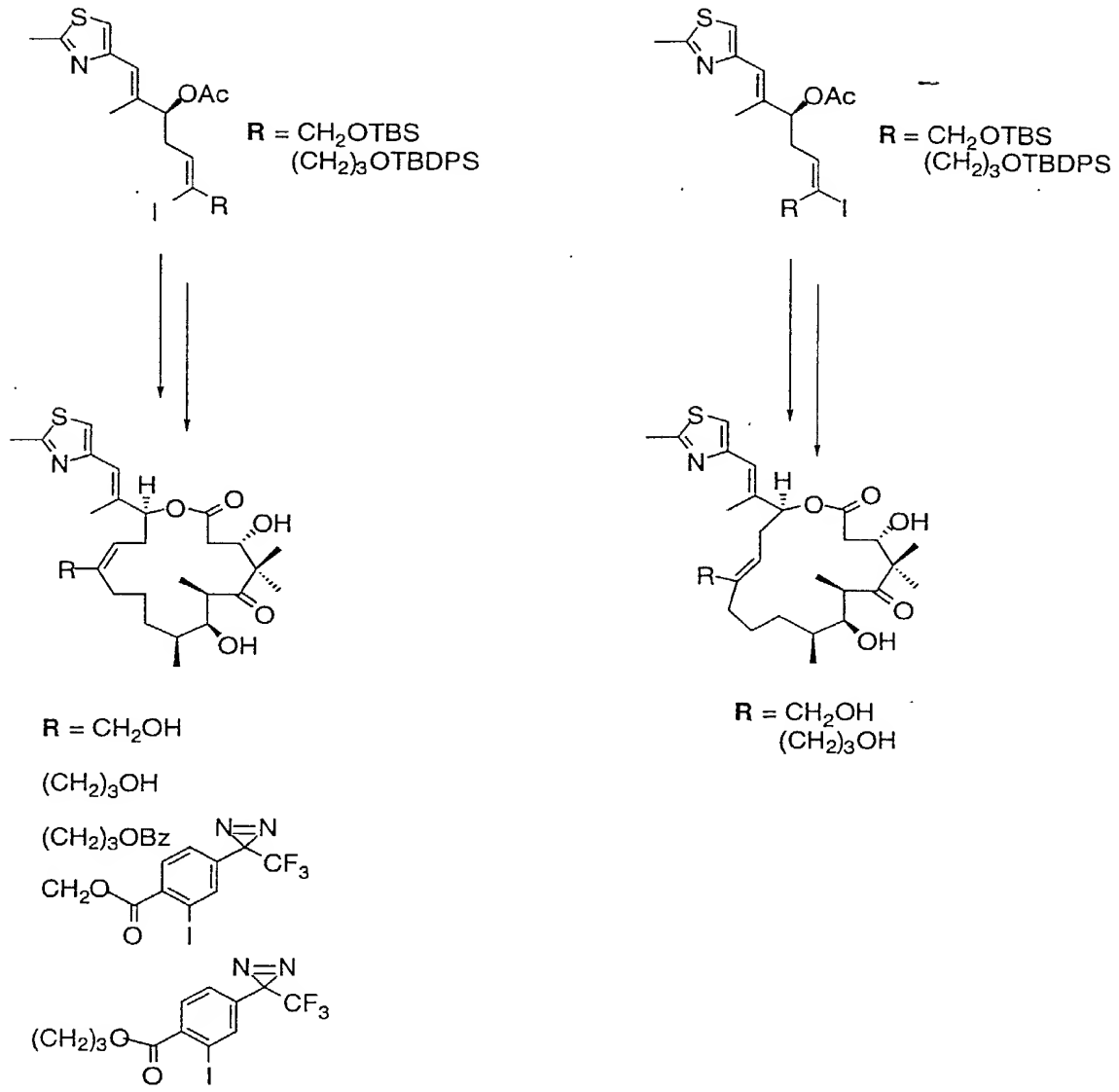

R = CH2OTBS
(CH2)3OTBDPS
R = CH2OTBS
(CH2)3OTBDPS
R = CH2OH
(CH2)3OH
R = CH2OH
(CH2)3OH
(CH2)3OBz
CH2O
CF3
(CH2)3O
CF3

Figure 2

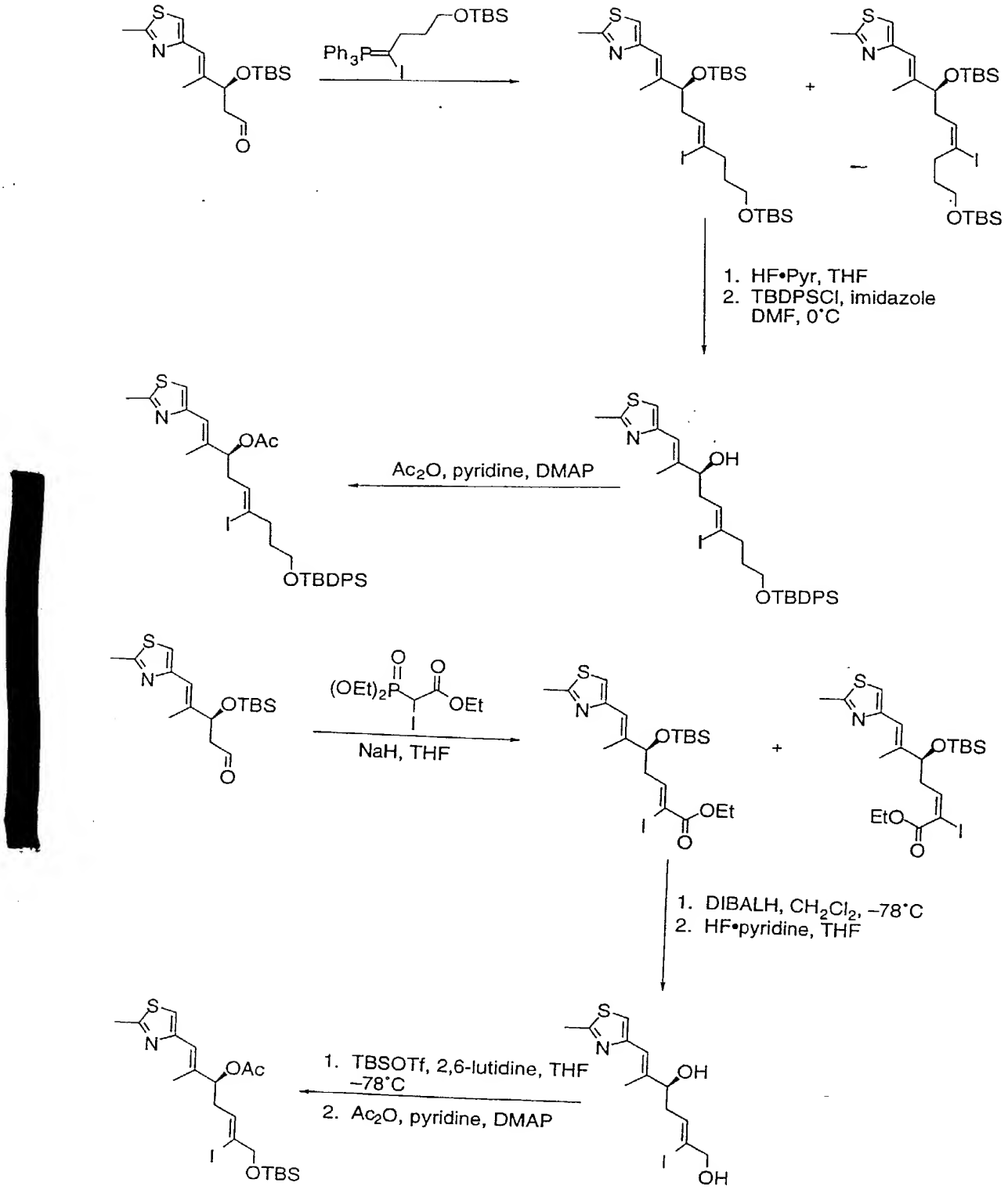


Figure 3(A)

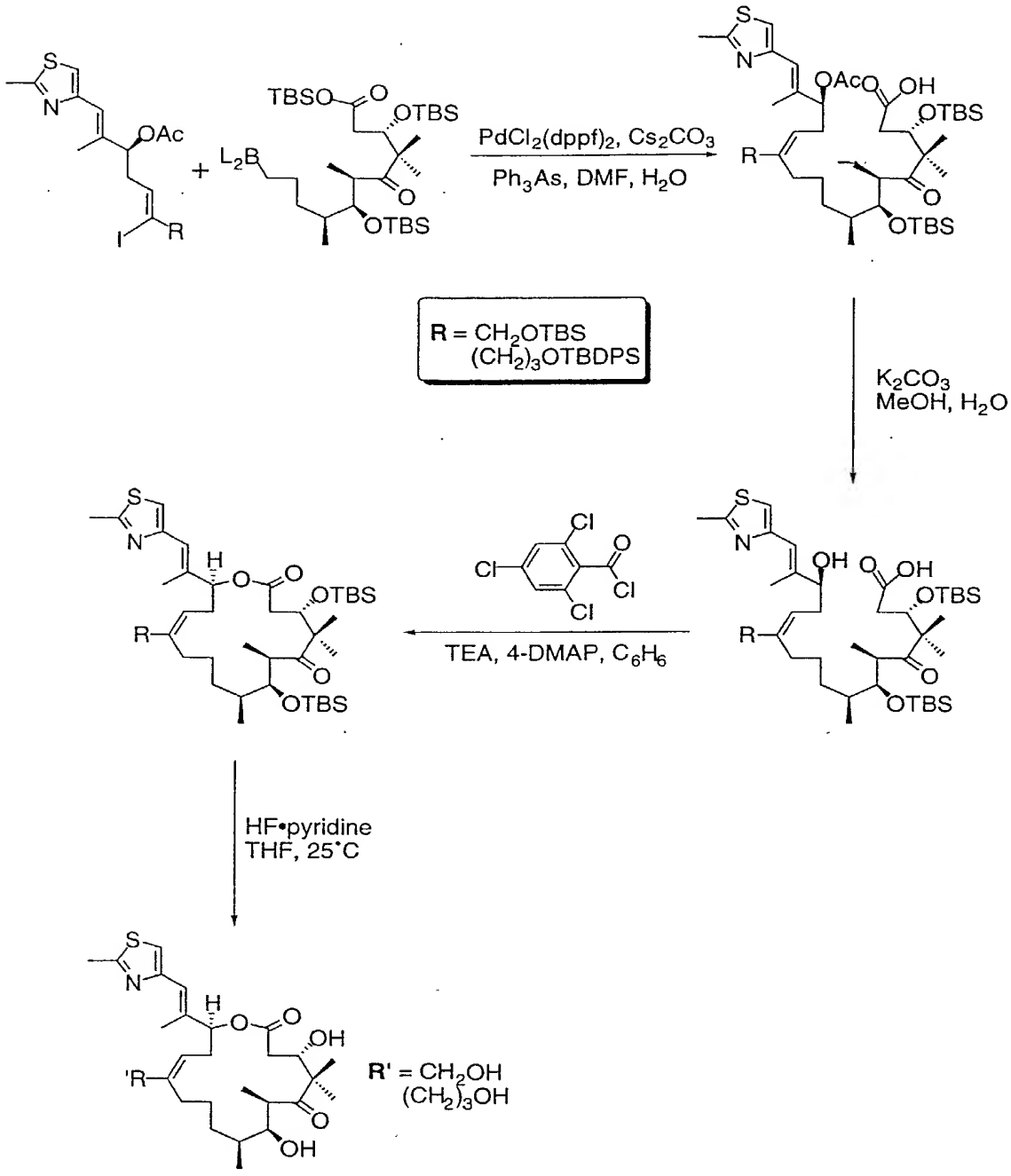
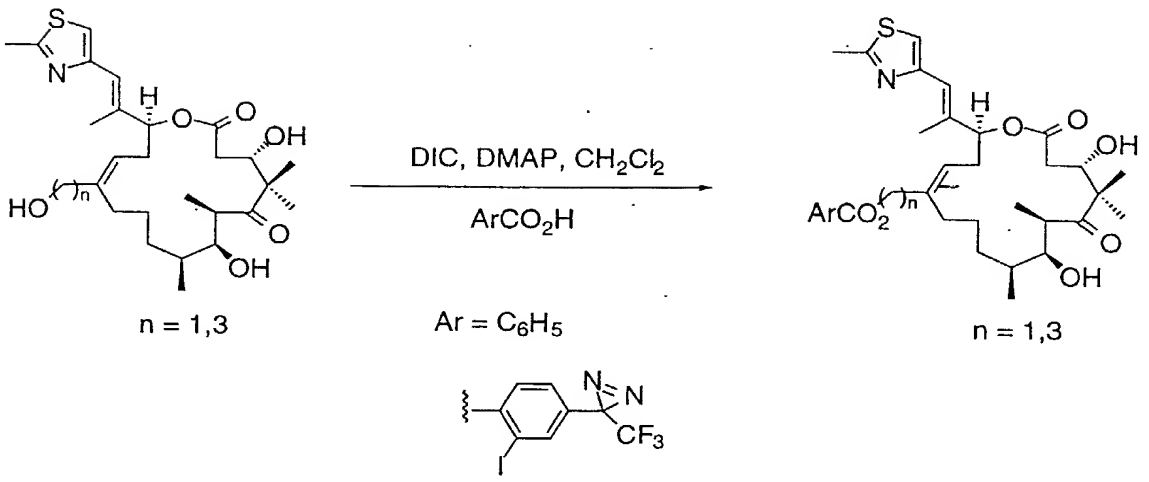

PdCl2(dppf)2, Cs2CO3
Ph3As, DMF, H2O
R = CH2OTBS
(CH2)3OTBDPS
K2CO3
MeOH, H2O
TEA, 4-DMAP, C6H6
HF•pyridine
THF, 25°C
R' = CH2OH
(CH2)3OH

Fig. 3(B)



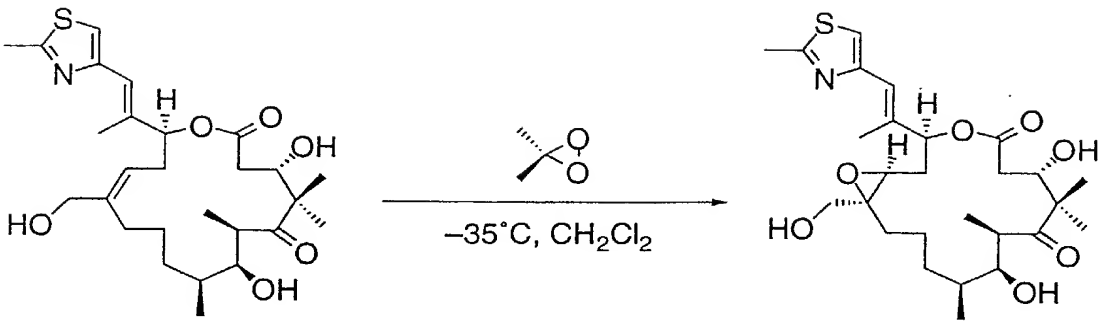


Fig. 3(C)

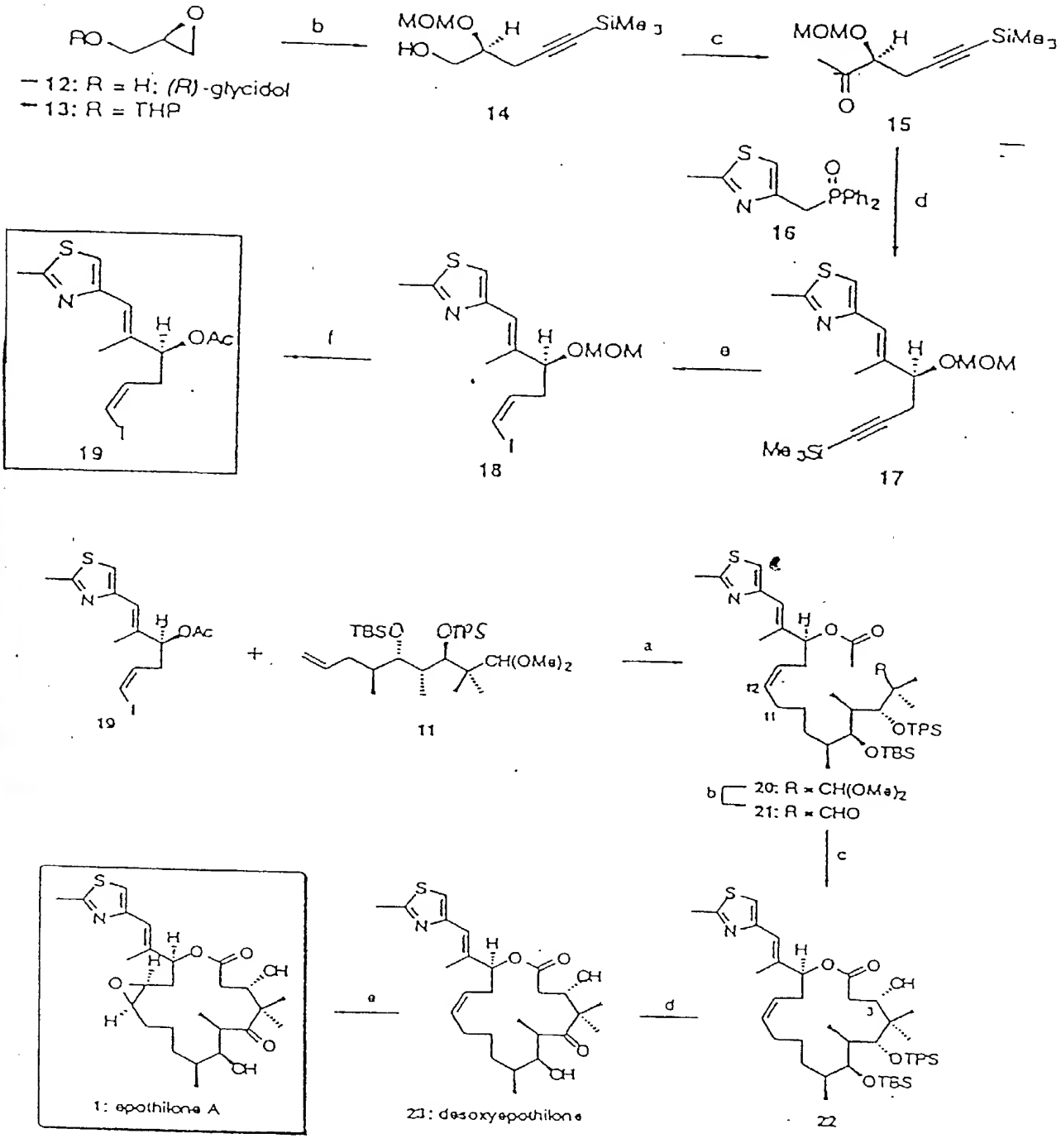

RO
12: R = H; (R)-glycidol
13: R = THP
b
MOMO
H
HO
SiMe3
14
c
MOMO
H
SiMe3
O
15
S
N
O
PPh2
16
d
S
N
H
OAc
I
19
f
S
N
H
OMOM
I
18
e
S
N
H
OMOM
Me3Si
17
S
N
H
OAc
I
19
+
TBSO
OTPS
CH(OMe)2
11
a
S
N
H
O
O
R
12
11
OTPS
OTBS
b
20: R = CH(OMe)2
21: R = CHO
c
S
N
H
O
O
OH
O
H
H
O
OH
1: epothilone A
e
S
N
H
O
O
OH
O
OH
23: desoxyepothilone
d
S
N
H
O
O
OH
3
OTPS
OTBS
22

Figure 4

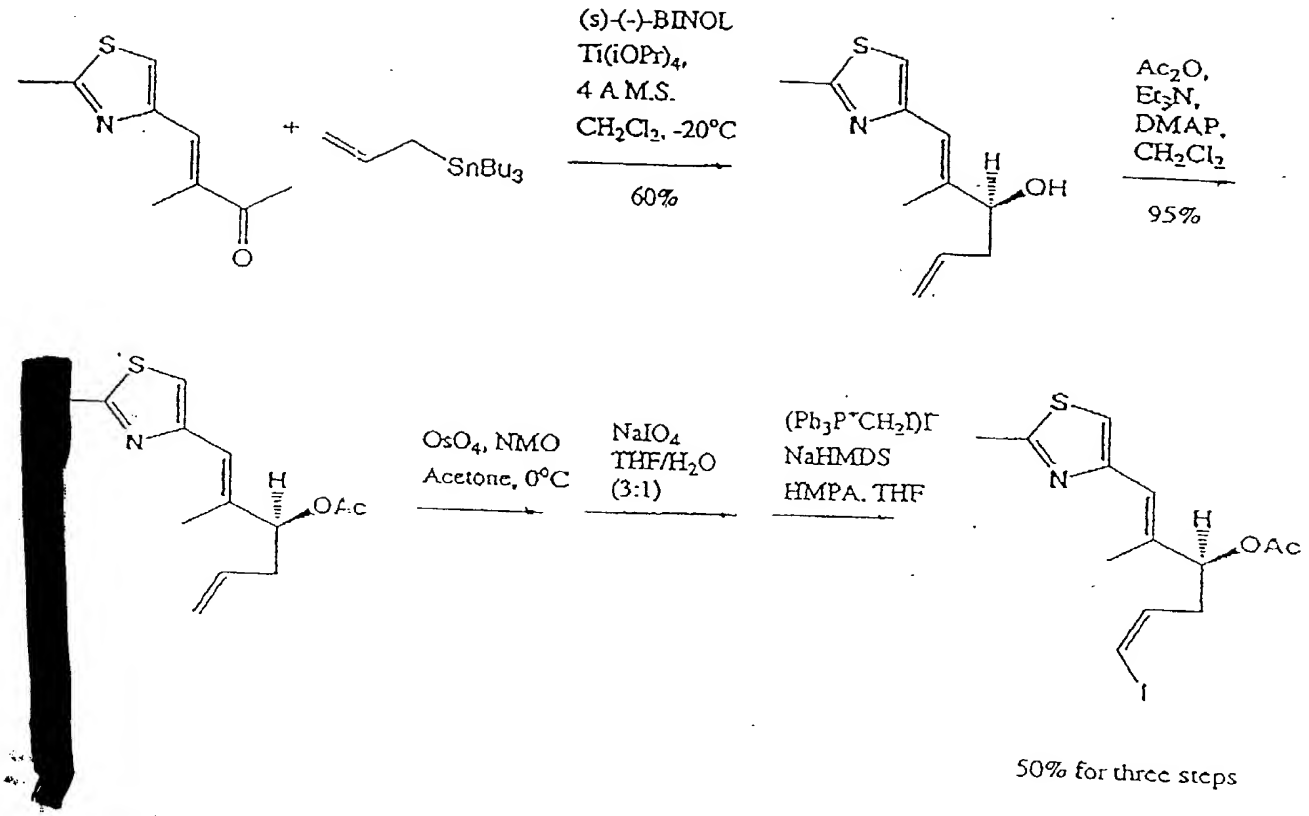
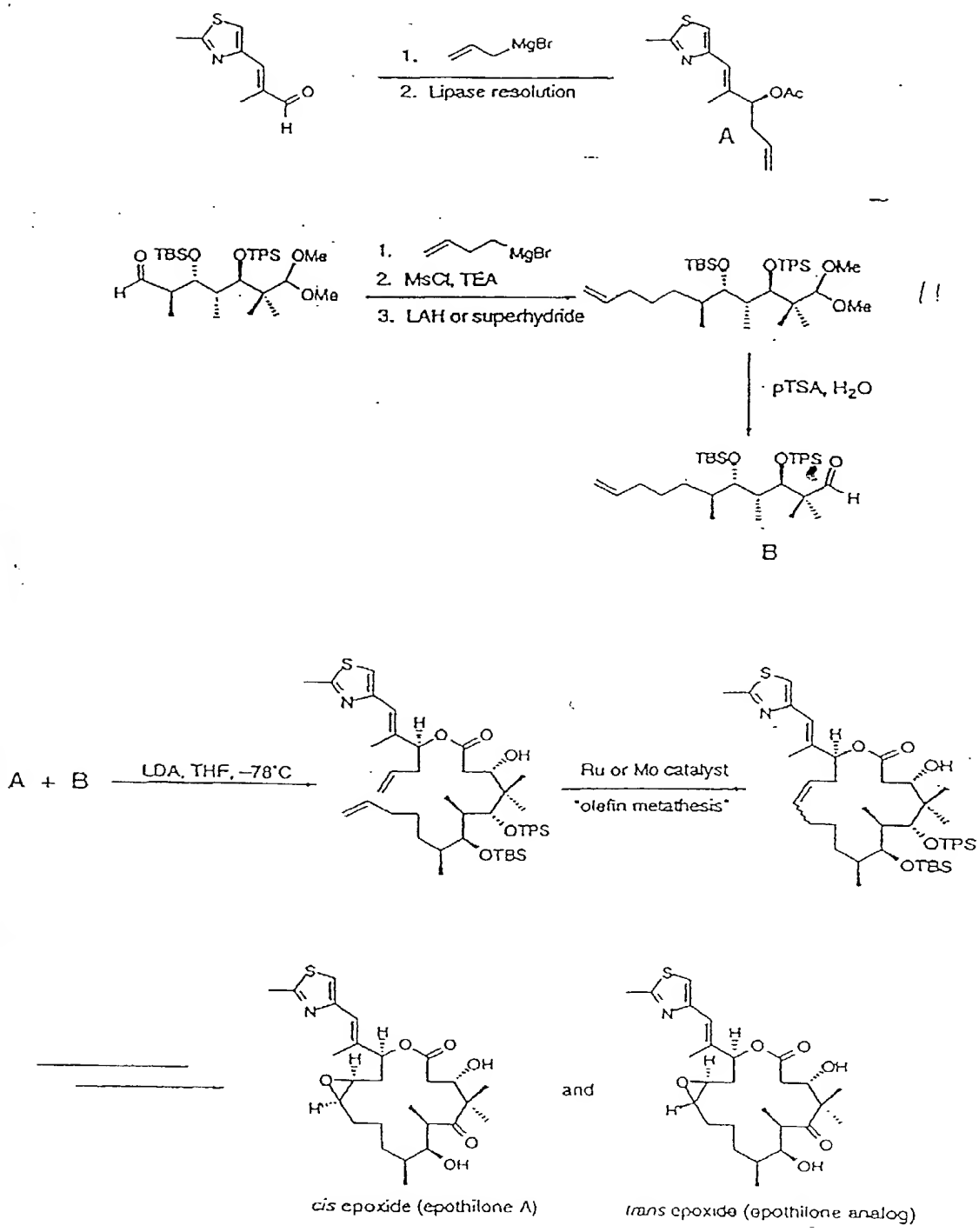
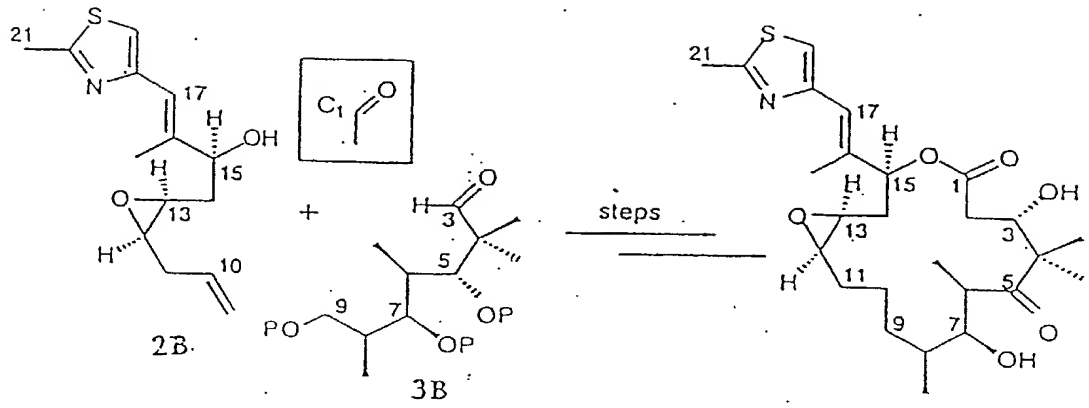

(s)-(-)-BINOL
Ti(iOPr)4,
4 A M.S.
CH2Cl2, -20°C
60%
Ac2O,
Et3N,
DMAP,
CH2Cl2
95%
OsO4, NMO
Acetone, 0°C
NaIO4
THF/H2O
(3:1)
(Ph3P+CH2I)I-
NaHMDS
HMPA. THF
50% for three steps

Figure 5



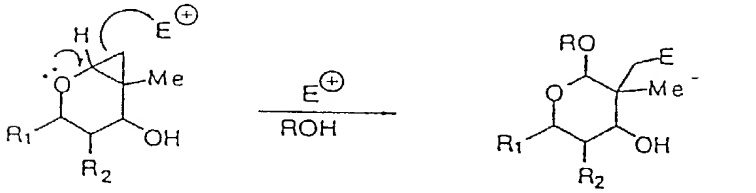
*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

Figure 6



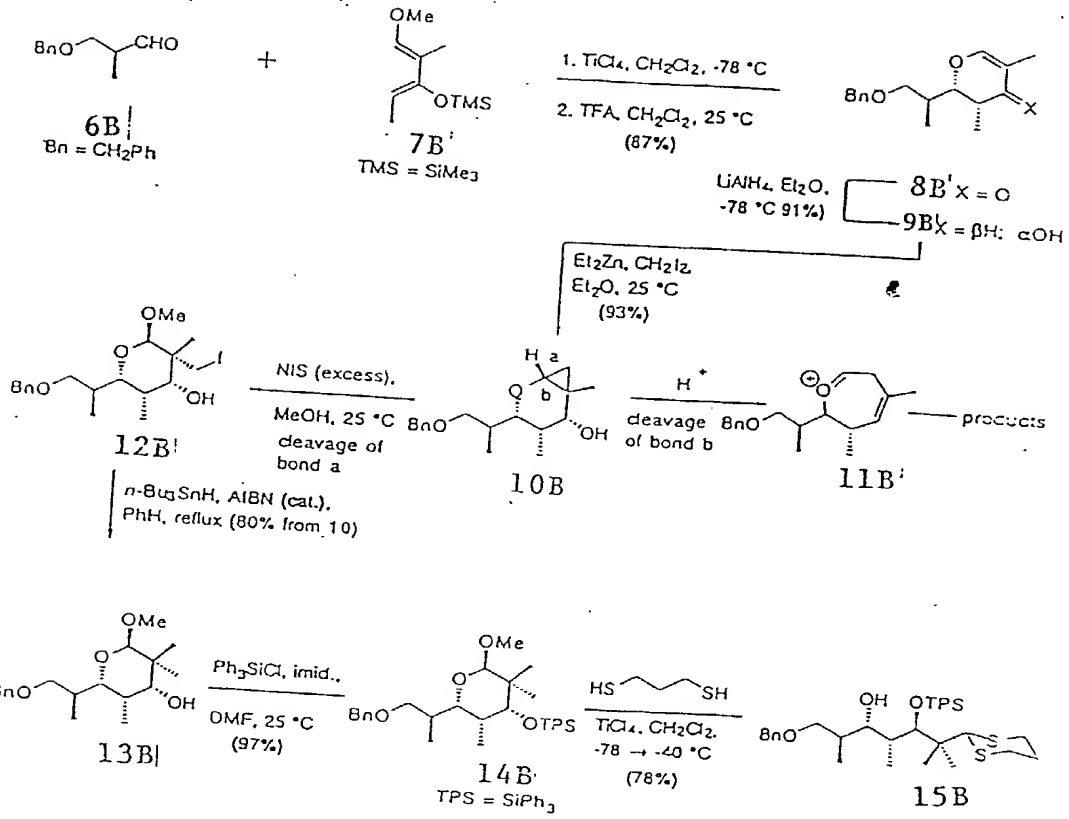
P = unspecified protecting group

Convergent strategy for a total synthesis of epothilone A (1).



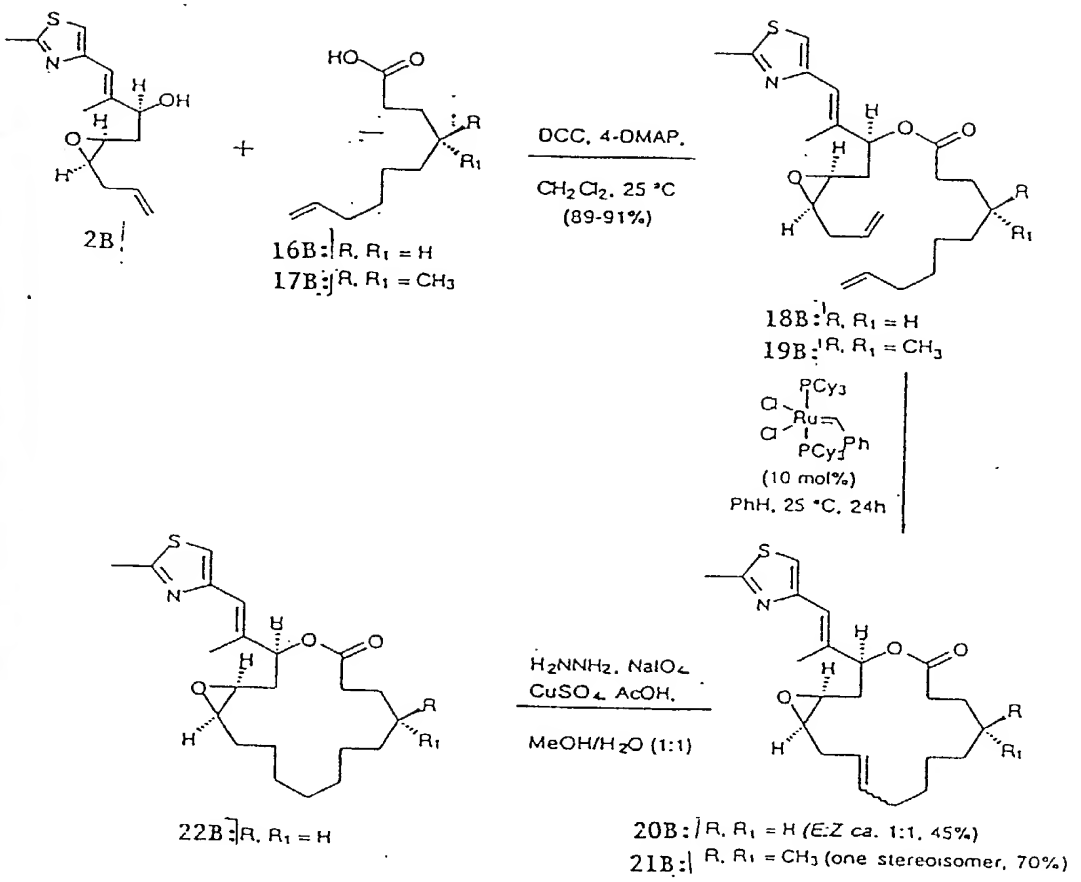
The glycal cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7



Enantioselective synthesis of compound 15B

Figure 8



Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9

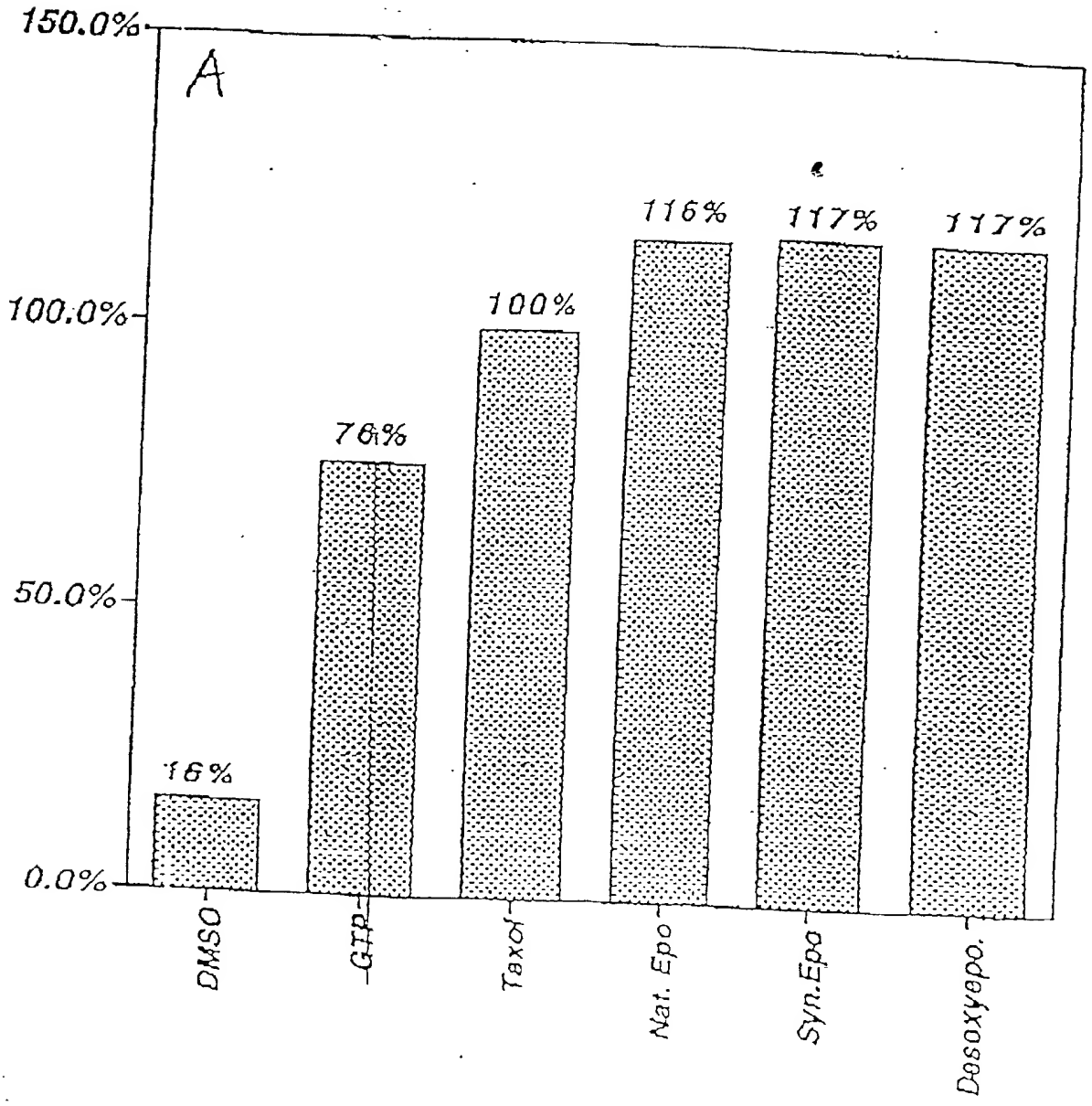


Figure 10

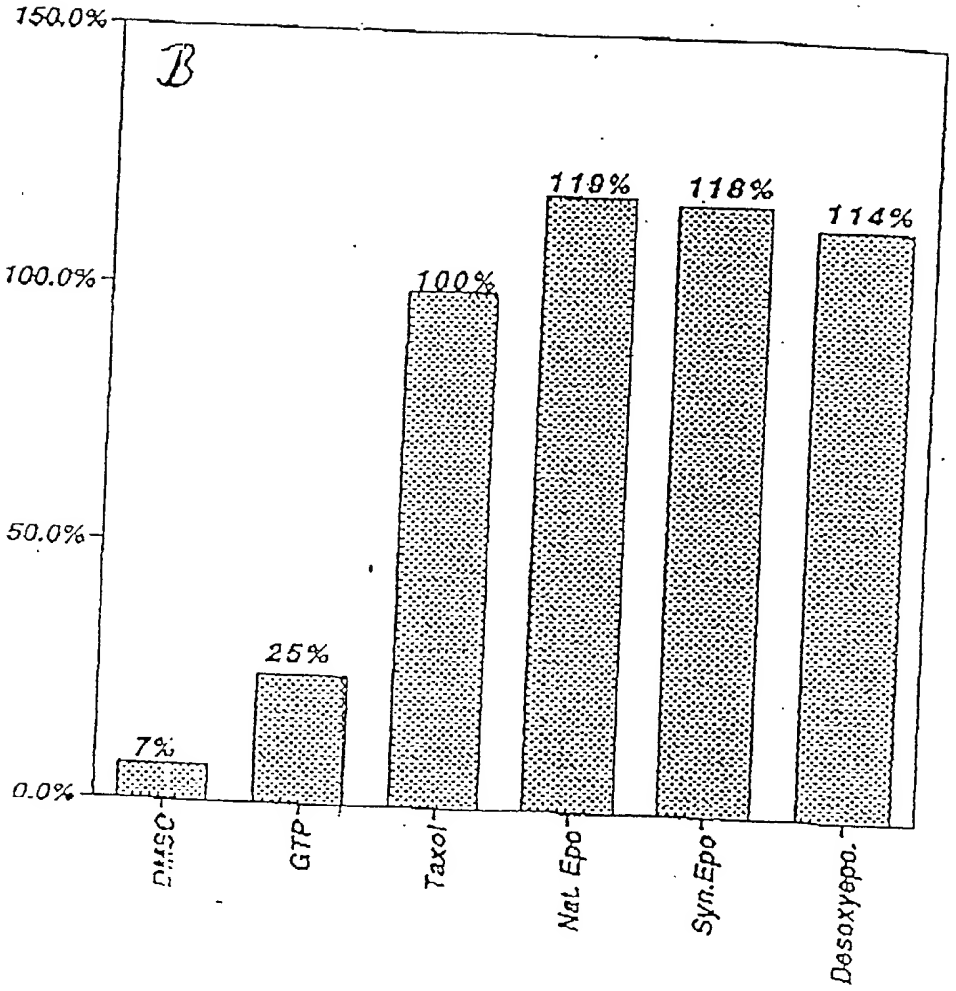
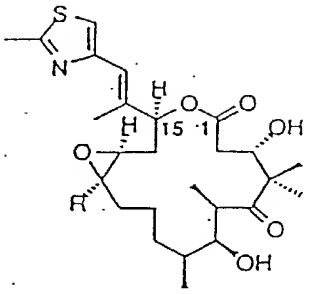


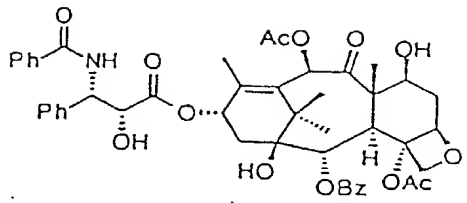
Figure 11

(A)



R = H; epothilone A
R = CH_3; epothilone B

(B)



1A: Taxol™

Figure 12

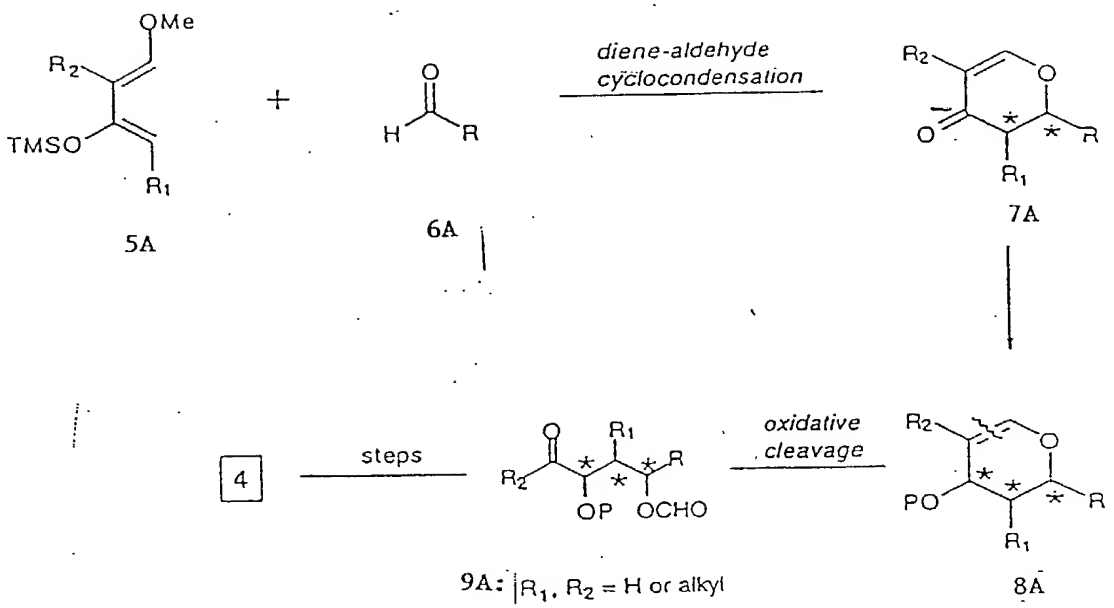

OMe
R2
TMSO
R1
5A
+
O
H
R
6A
diene-aldehyde
cyclocondensation
R2
O
O
R
R1
7A
4
steps
R1
O
R2
R
OP
OCHO
9A: R1, R2 = H or alkyl
oxidative
cleavage
R2
O
PO
R
R1
8A

Figure 13

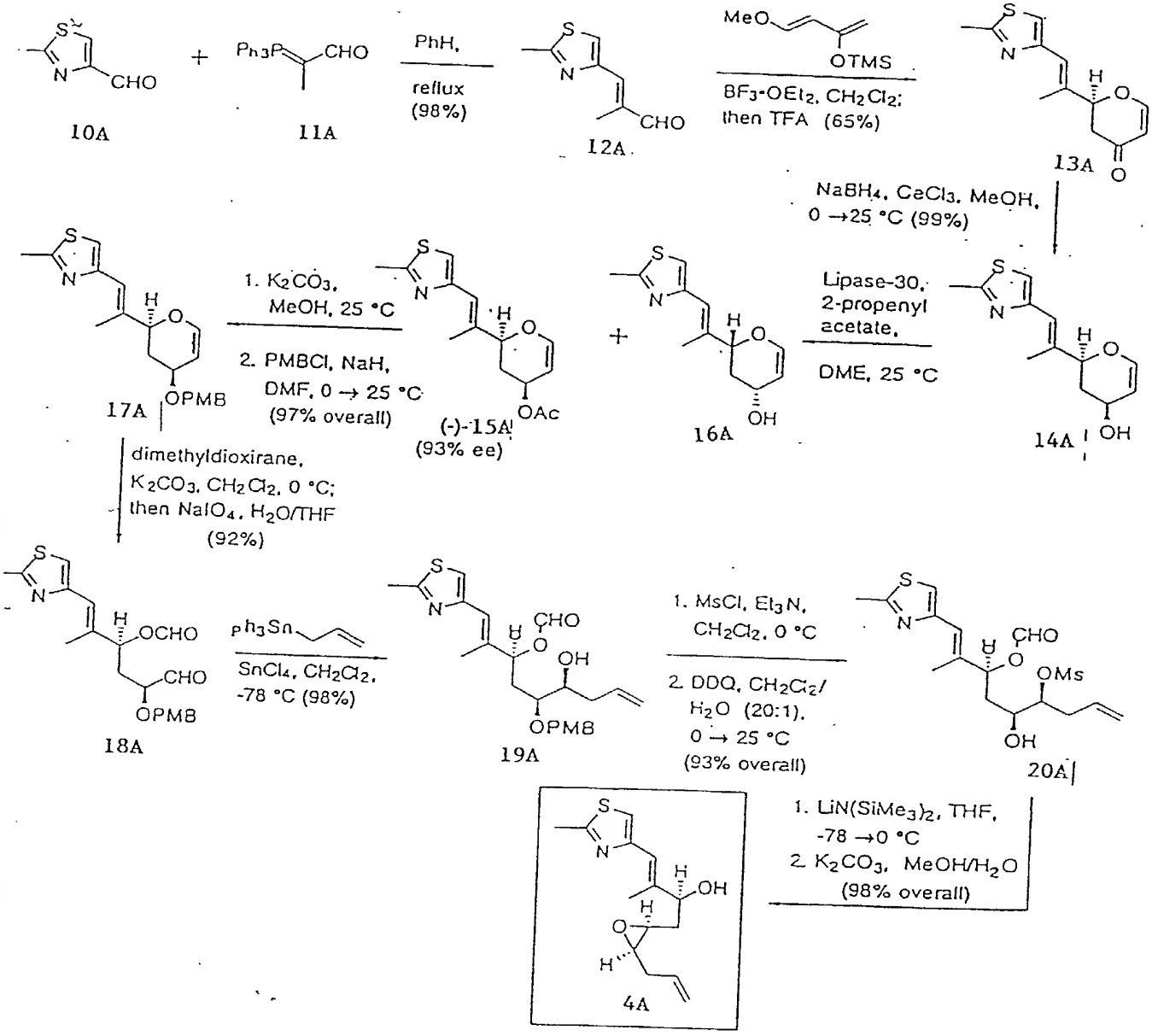

10A
11A
PhH, reflux (98%)
12A
MeO
OTMS
BF3·OEt2, CH2Cl2; then TFA (65%)
13A
NaBH4, CeCl3, MeOH, 0 →25 °C (99%)
1. K2CO3, MeOH, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C (97% overall)
17A
(-)-15A (93% ee)
16A
Lipase-30, 2-propenyl acetate, DME, 25 °C
14A
dimethyldioxirane, K2CO3, CH2Cl2, 0 °C; then NaIO4, H2O/THF (92%)
18A
Ph3Sn
SnCl4, CH2Cl2, -78 °C (98%)
19A
1. MsCl, Et3N, CH2Cl2, 0 °C
2. DDQ, CH2Cl2/H2O (20:1), 0 → 25 °C (93% overall)
20A
1. LiN(SiMe3)2, THF, -78 →0 °C
2. K2CO3, MeOH/H2O (98% overall)
4A

Figure 14

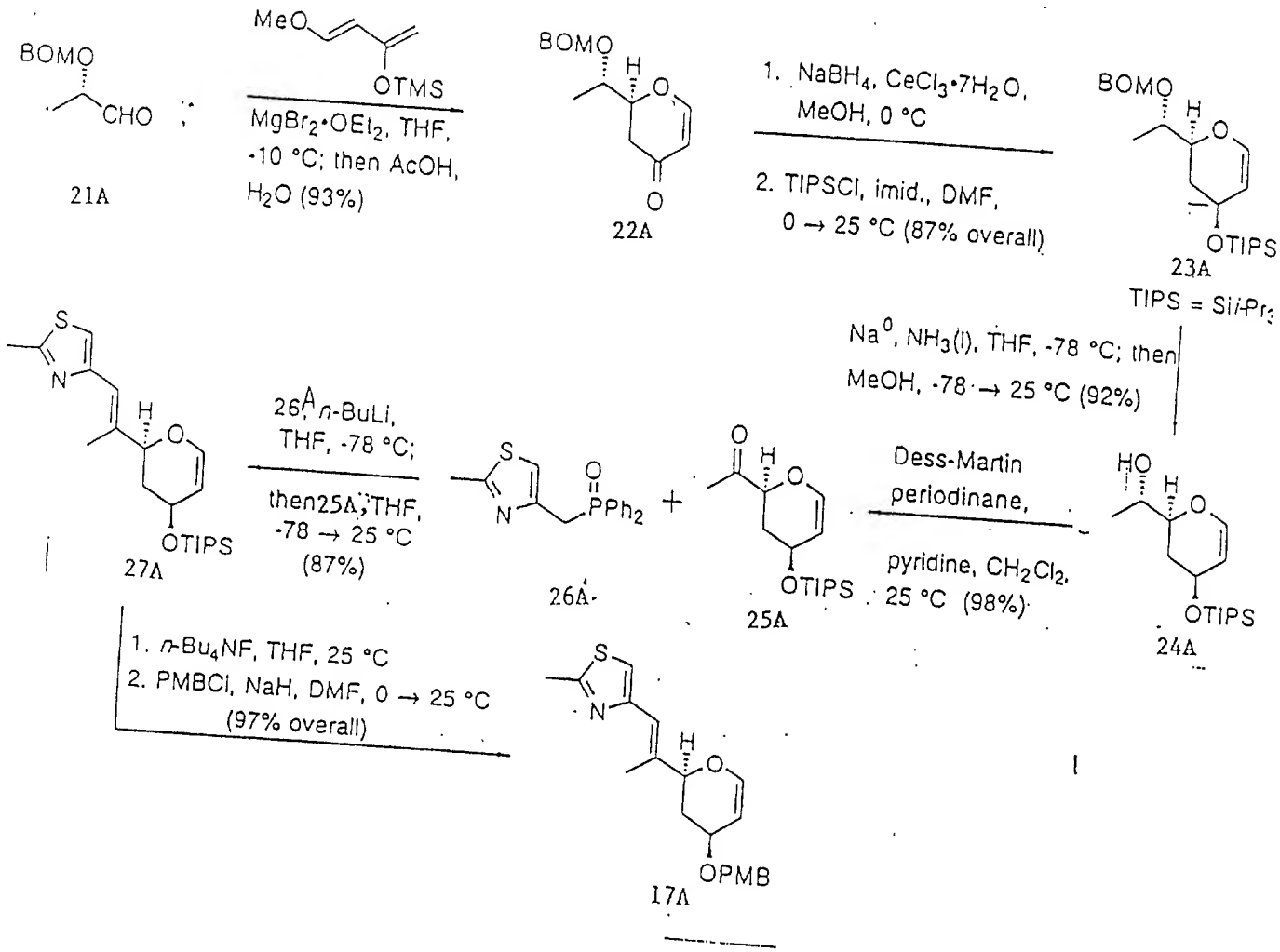

BOMO
CHO
21A
MeO
OTMS
MgBr2•OEt2, THF, -10 °C; then AcOH, H2O (93%)
BOMO
O
O
22A
1. NaBH4, CeCl3•7H2O, MeOH, 0 °C
2. TIPSCl, imid., DMF, 0 → 25 °C (87% overall)
BOMO
OTIPS
23A
TIPS = SiiPr3
Na0, NH3(l), THF, -78 °C; then MeOH, -78 → 25 °C (92%)
HO
OTIPS
24A
Dess-Martin periodinane, pyridine, CH2Cl2, 25 °C (98%)
O
OTIPS
25A
S
N
PPh2
O
26A
26A n-BuLi, THF, -78 °C; then 25A, THF, -78 → 25 °C (87%)
S
N
OTIPS
27A
1. n-Bu4NF, THF, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C (97% overall)
S
N
OPMB
17A

Figure 15

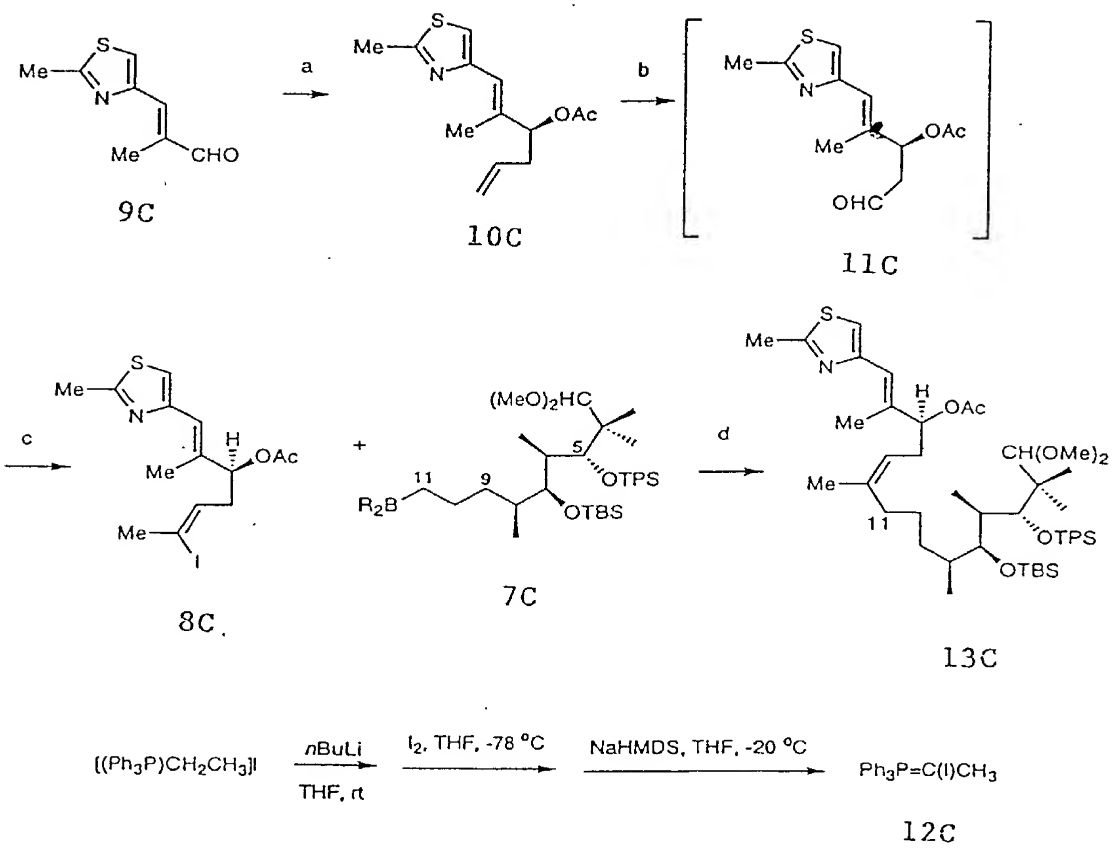

Me
S
N
Me
CHO
9C
a
10C
OAc
b
11C
OHC
c
H
8C
Me
I
+
(MeO)2HC
5
OTPS
11
9
R2B
OTBS
7C
d
CH(OMe)2
13C
[(Ph3P)CH2CH3]I
nBuLi
THF, rt
I2, THF, -78 °C
NaHMDS, THF, -20 °C
Ph3P=C(I)CH3
12C

Figure 16

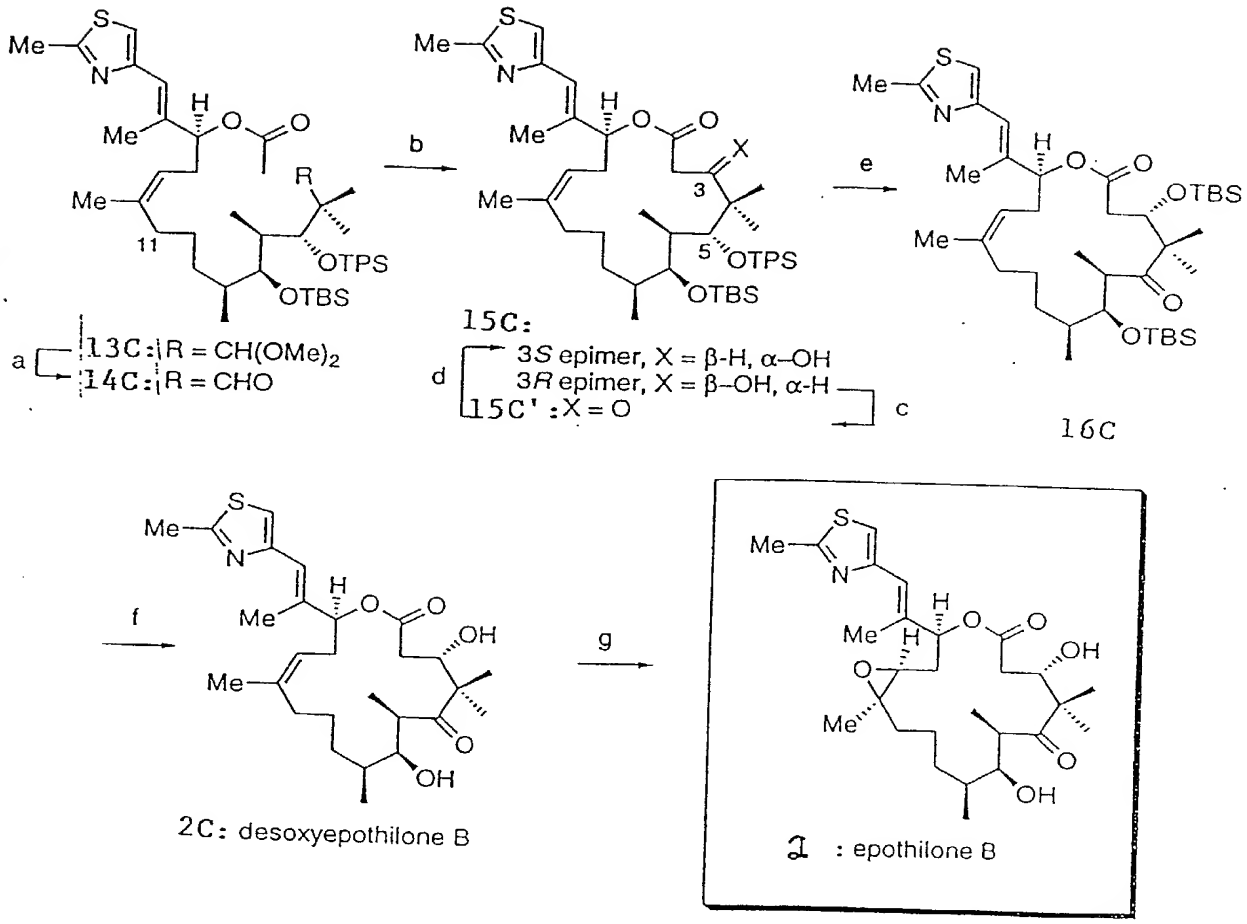


Figure 17

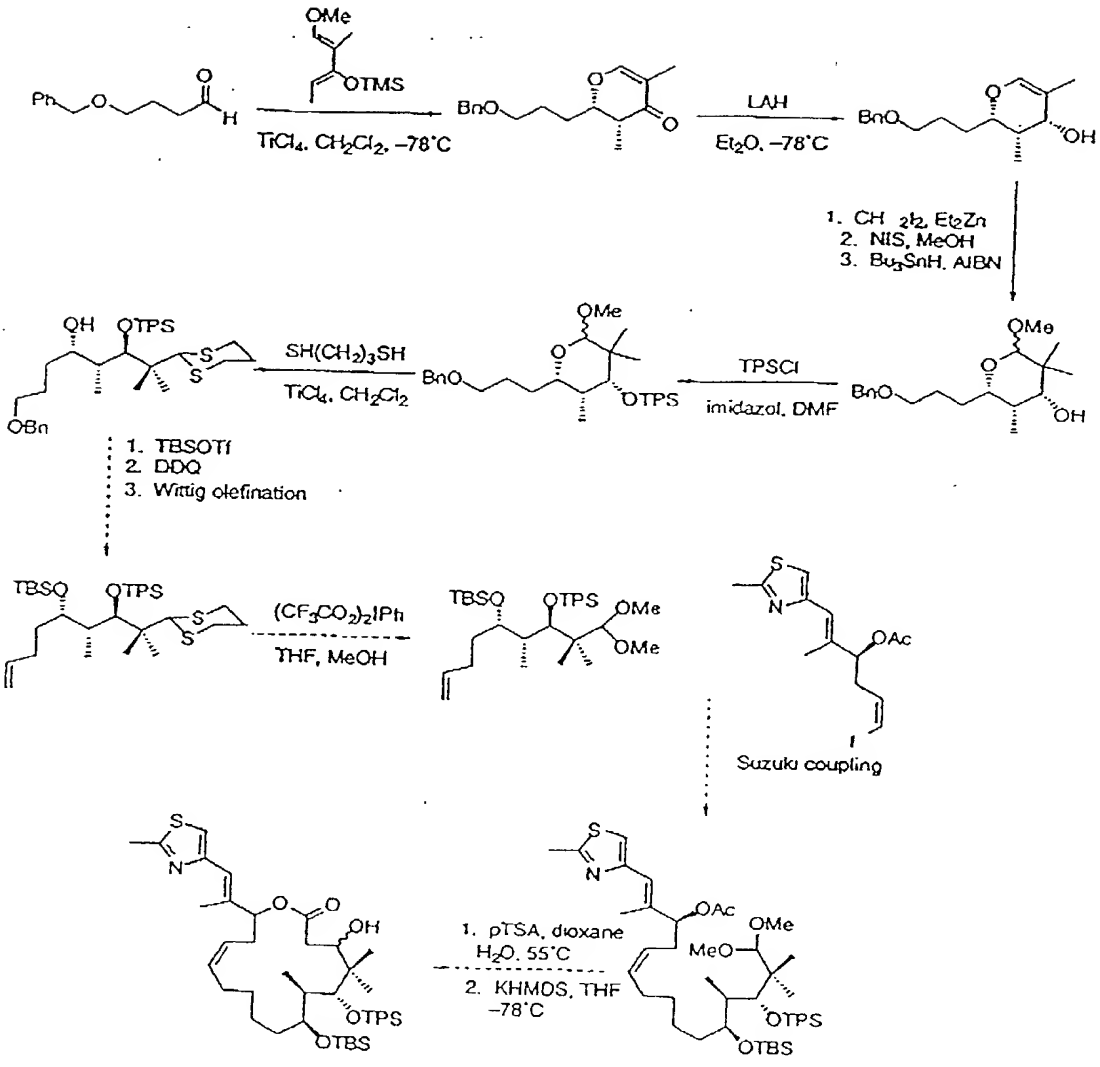


Figure 18

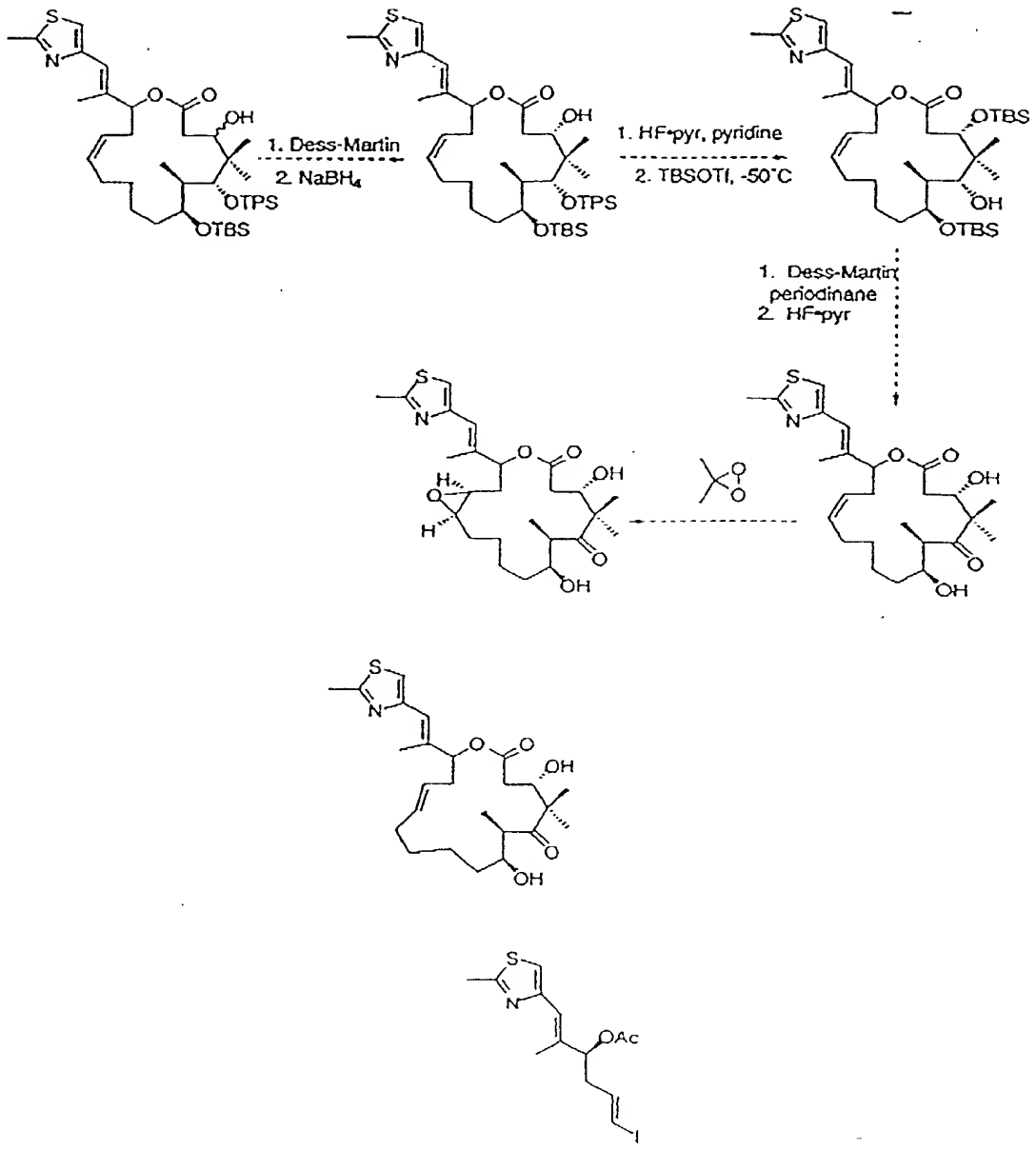
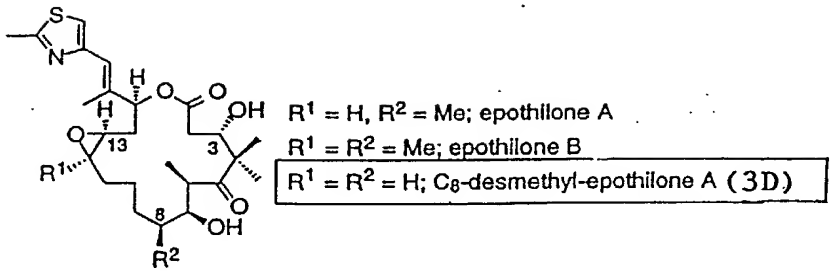


Figure 19



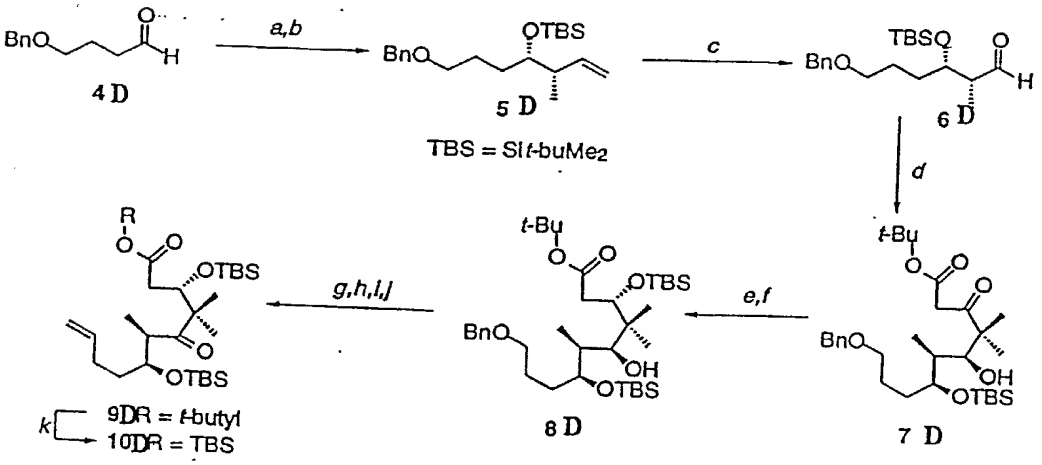


FIGURE 20

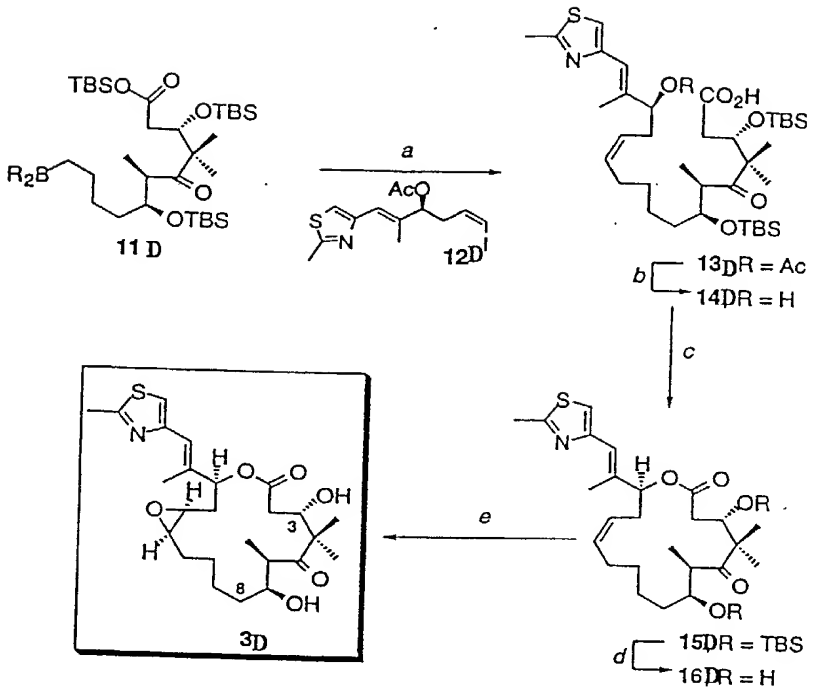


FIGURE 21

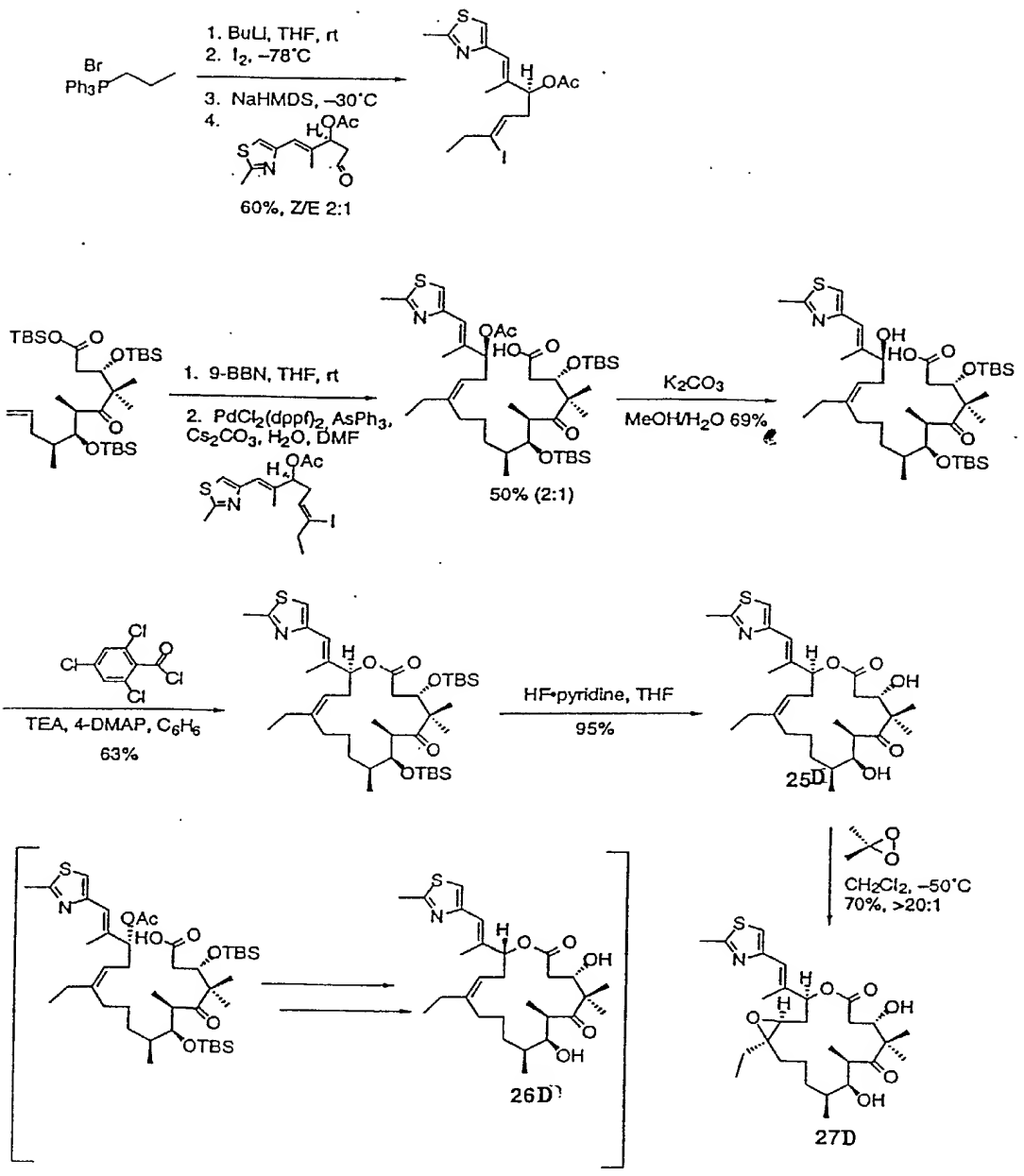


FIGURE 22

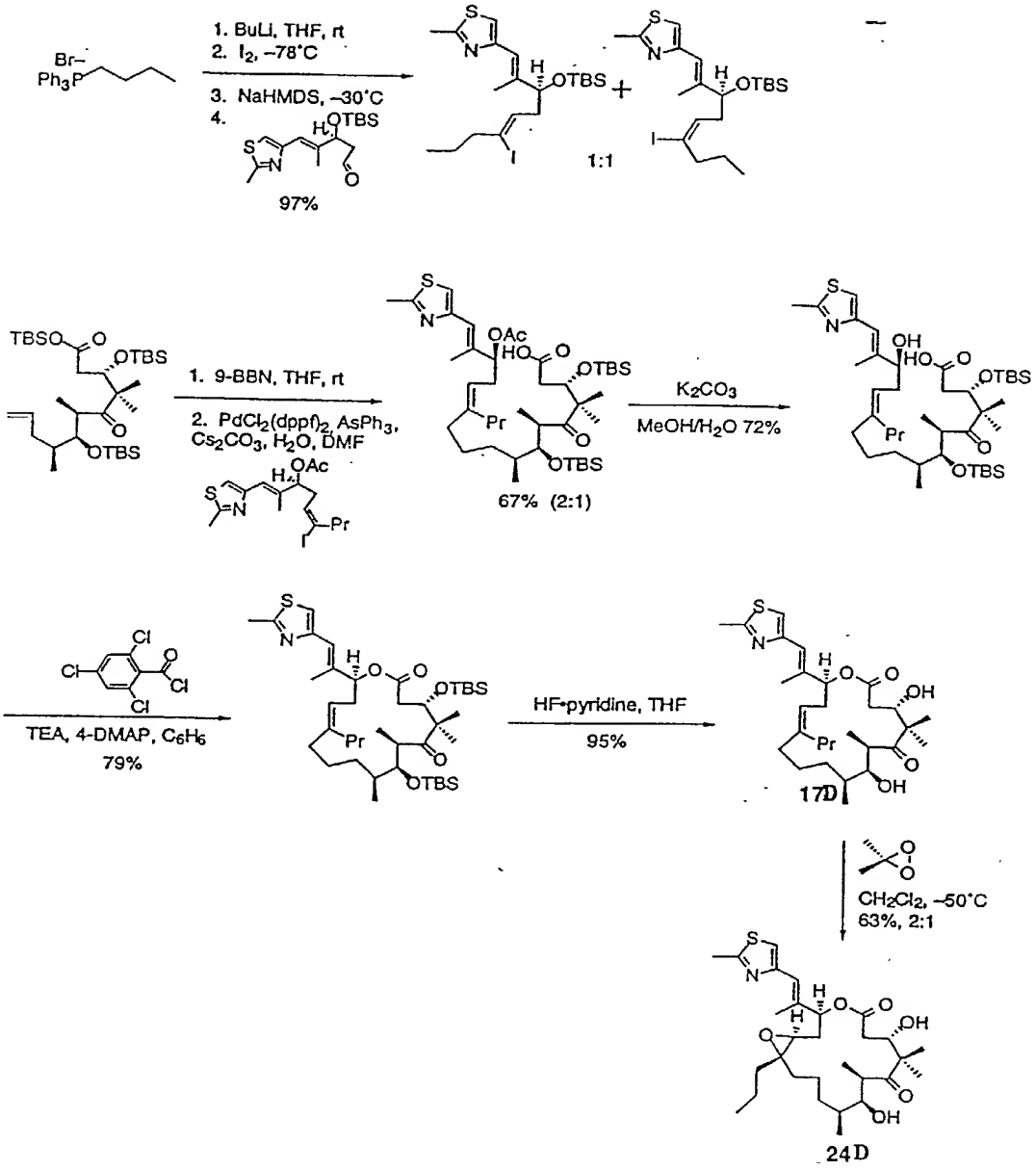

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
97%
1:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
67% (2:1)
K2CO3
MeOH/H2O 72%
TEA, 4-DMAP, C6H6
79%
HF•pyridine, THF
95%
17D
CH2Cl2, –50°C
63%, 2:1
24D

FIGURE 23

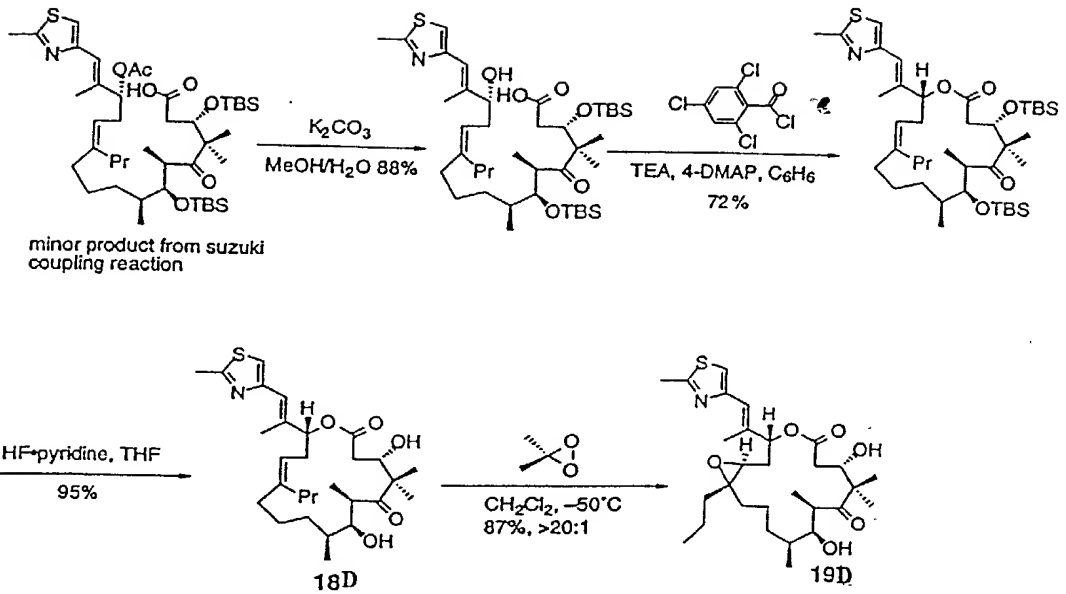

OAc
OTBS
Pr
OTBS
minor product from suzuki coupling reaction
K_2CO_3
MeOH/H_2O 88%
OH
OTBS
Pr
OTBS
Cl
Cl
Cl
TEA, 4-DMAP, C_6H_6
72%
H
OTBS
Pr
OTBS
HF•pyridine, THF
95%
H
OH
Pr
OH
18D
CH_2Cl_2, –50°C
87%, >20:1
H
H
OH
OH
19D

FIGURE 24

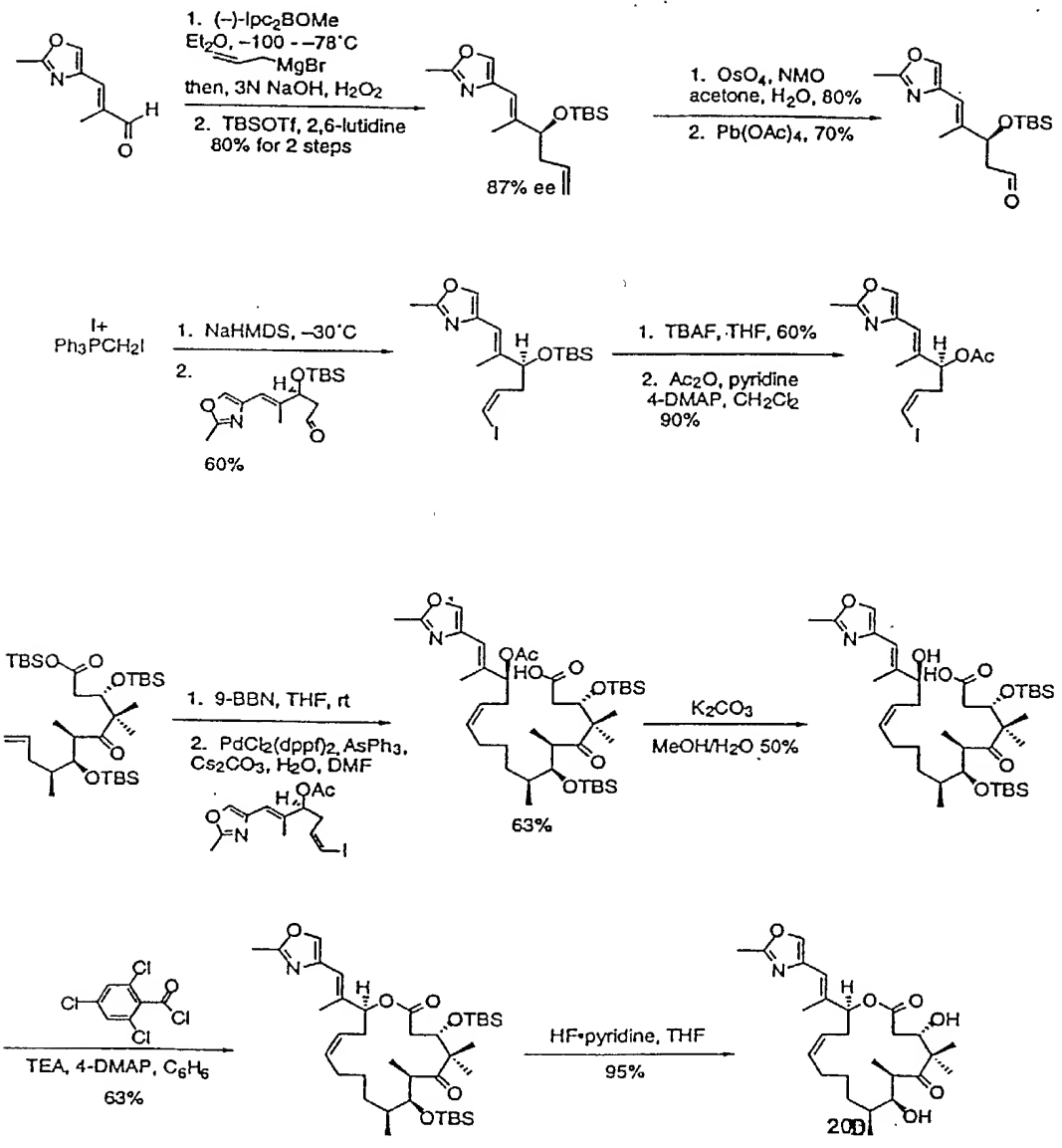


FIGURE 25

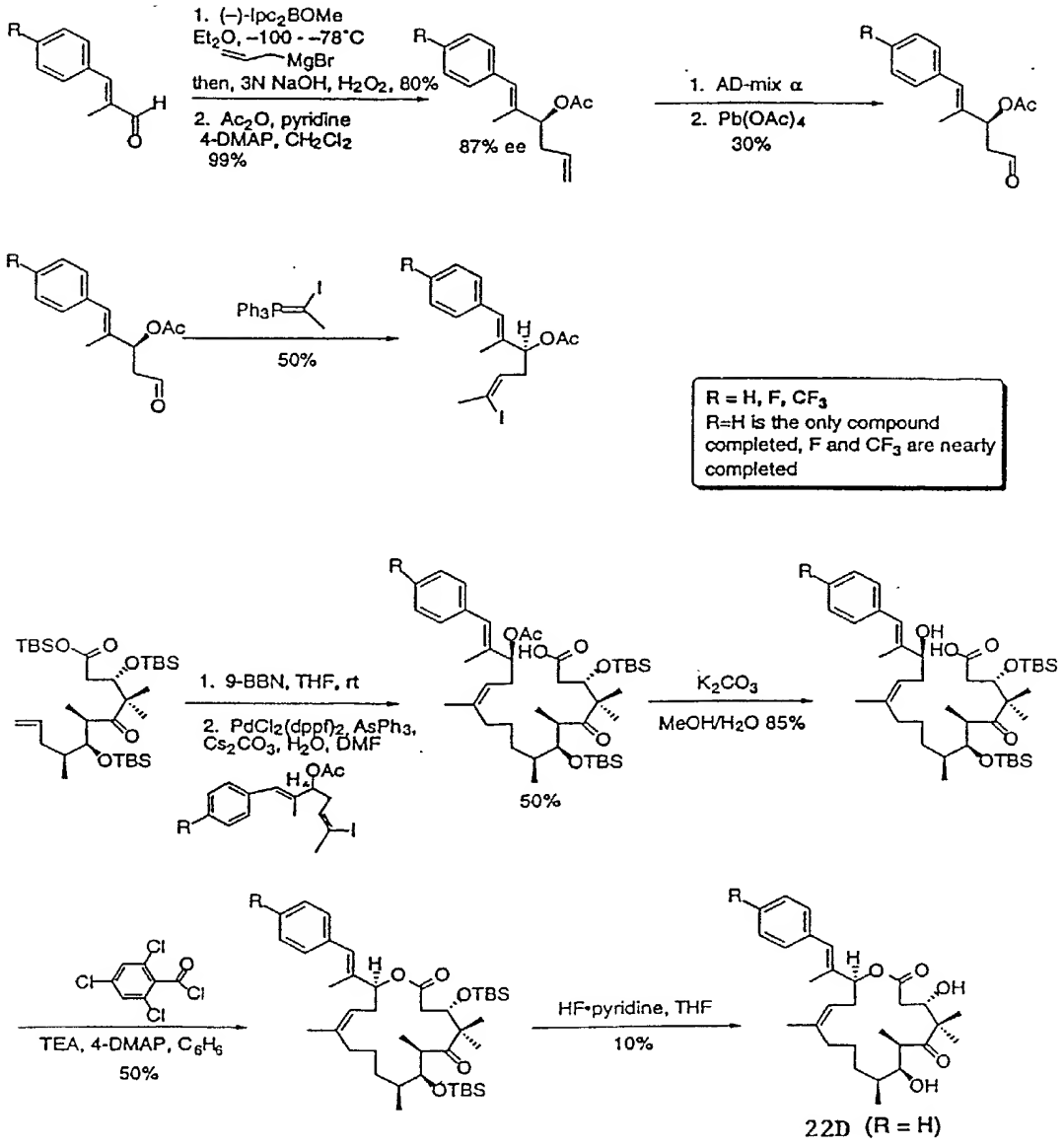

1. (–)-Ipc2BOMe
Et2O, –100 - –78°C
MgBr
then, 3N NaOH, H2O2, 80%
2. Ac2O, pyridine
4-DMAP, CH2Cl2
99%
87% ee
1. AD-mix α
2. Pb(OAc)4
30%
Ph3P
50%
R = H, F, CF3
R=H is the only compound completed, F and CF3 are nearly completed
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
50%
K2CO3
MeOH/H2O 85%
TEA, 4-DMAP, C6H6
50%
HF•pyridine, THF
10%
22D (R = H)

FIGURE 26

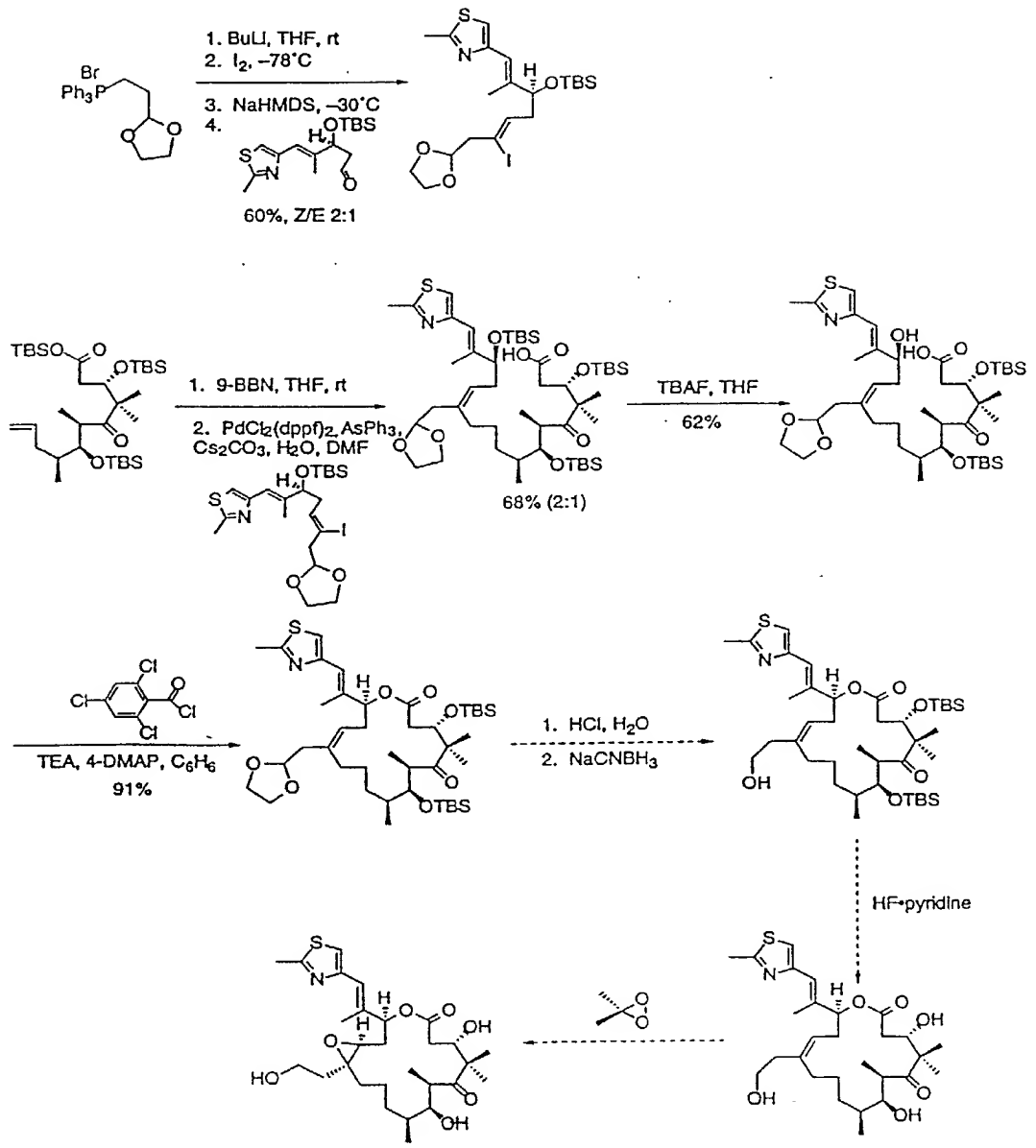
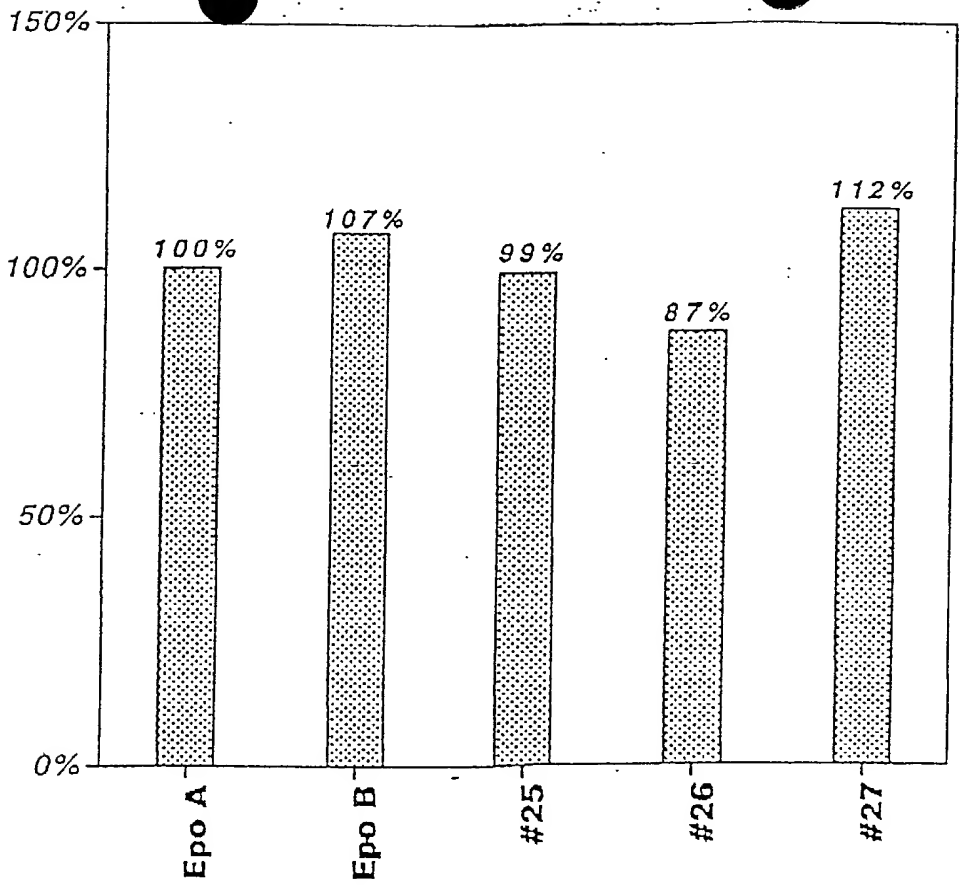

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
68% (2:1)
TBAF, THF
62%
TEA, 4-DMAP, C6H6
91%
1. HCl, H2O
2. NaCNBH3
HF•pyridine

FIGURE 27


150%
100%
50%
0%
100%
107%
99%
87%
112%
Epo A
Epo B
#25
#26
#27

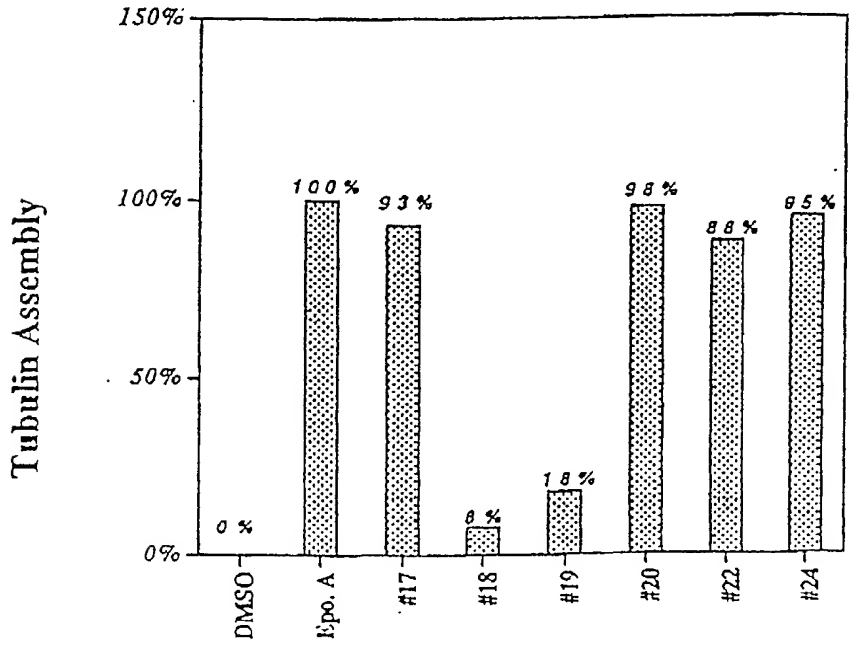

Tubulin Assembly
150%
100%
50%
0%
0 %
100%
93%
8 %
18%
98%
88%
95%
DMSO
Epo. A
#17
#18
#19
#20
#22
#24

FIGURE 28

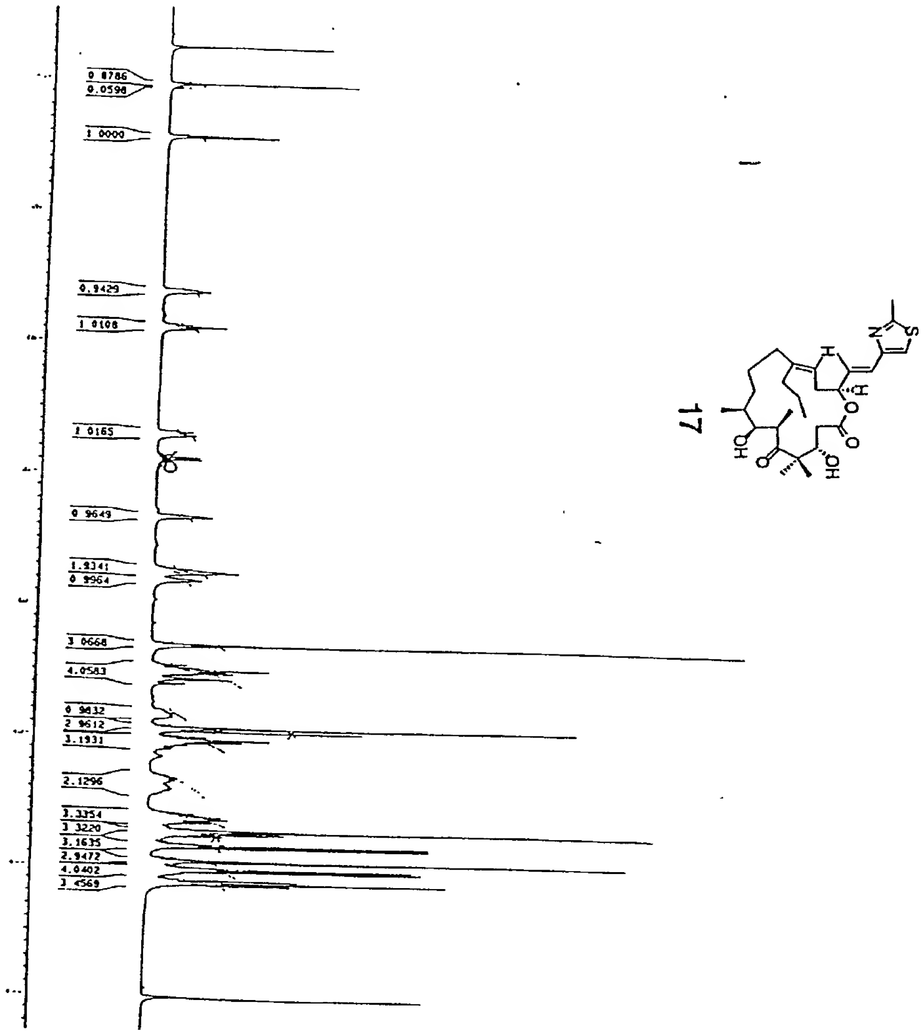
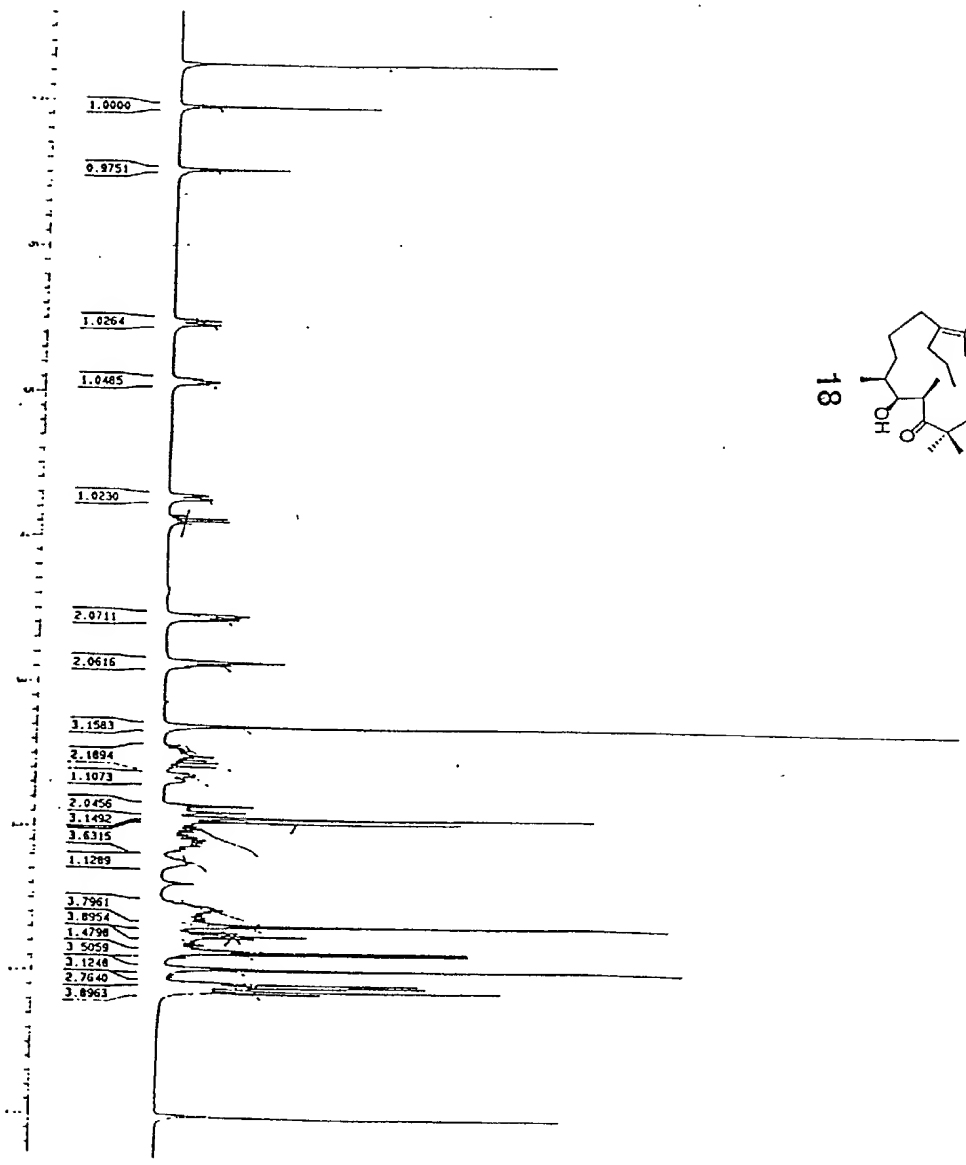


FIGURE 29


1.0000
0.9751
1.0264
1.0485
1.0230
2.0711
2.0616
3.1583
2.1894
1.1073
2.0456
3.1492
3.6315
1.1289
3.7961
3.8954
1.4798
3.5059
3.1248
2.7640
3.8963

18

FIGURE 30

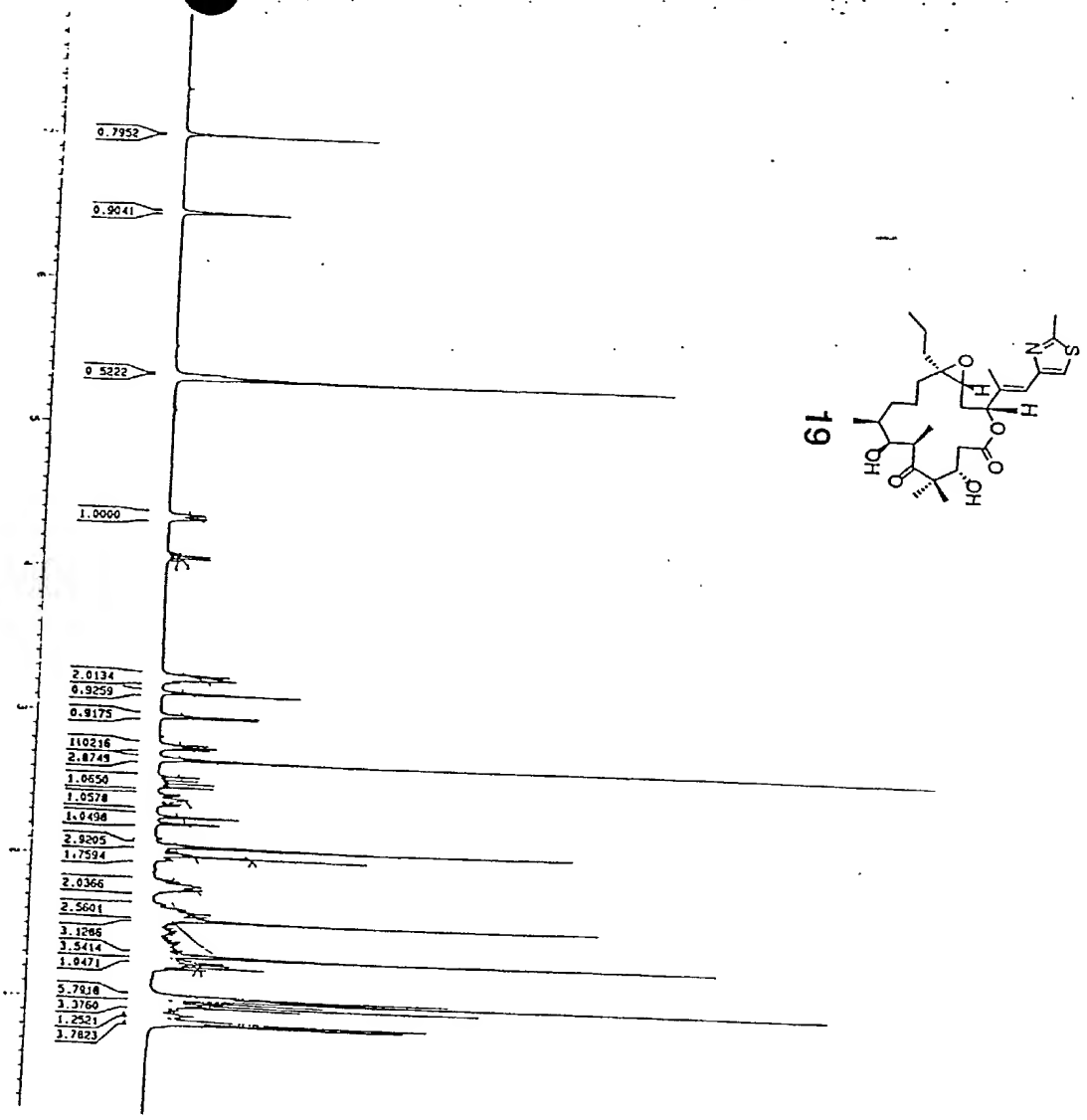

0.7952
0.9041
0.5222
1.0000
2.0134
0.9259
0.9175
1.0236
2.8749
1.0650
1.0578
1.0498
2.9205
1.7594
2.0366
2.5601
3.1286
3.5414
1.0471
5.7918
3.3760
1.2521
3.7823
19
N
S
O
H
H
O
HO
O
O
HO

FIGURE 31

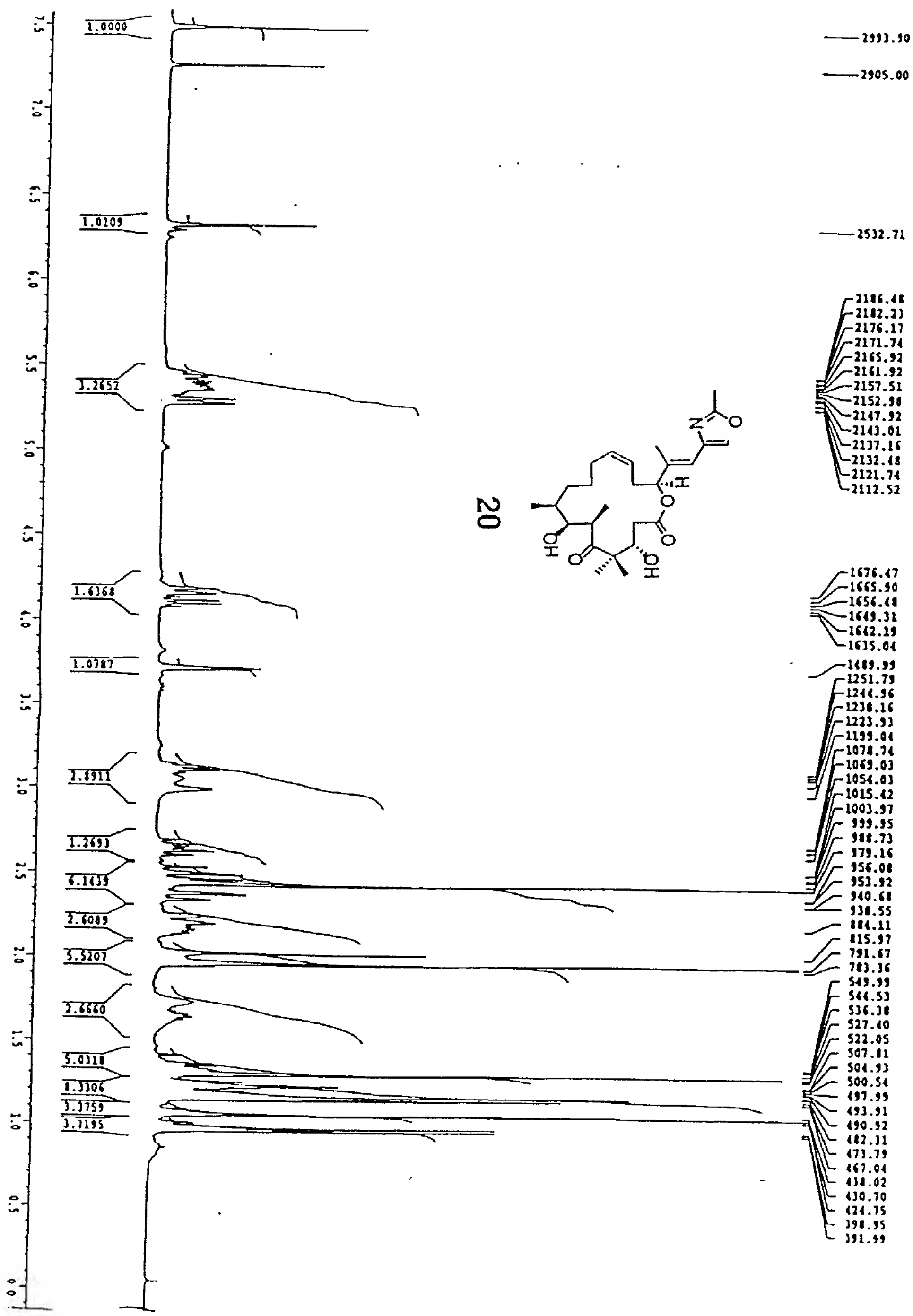


FIGURE 32

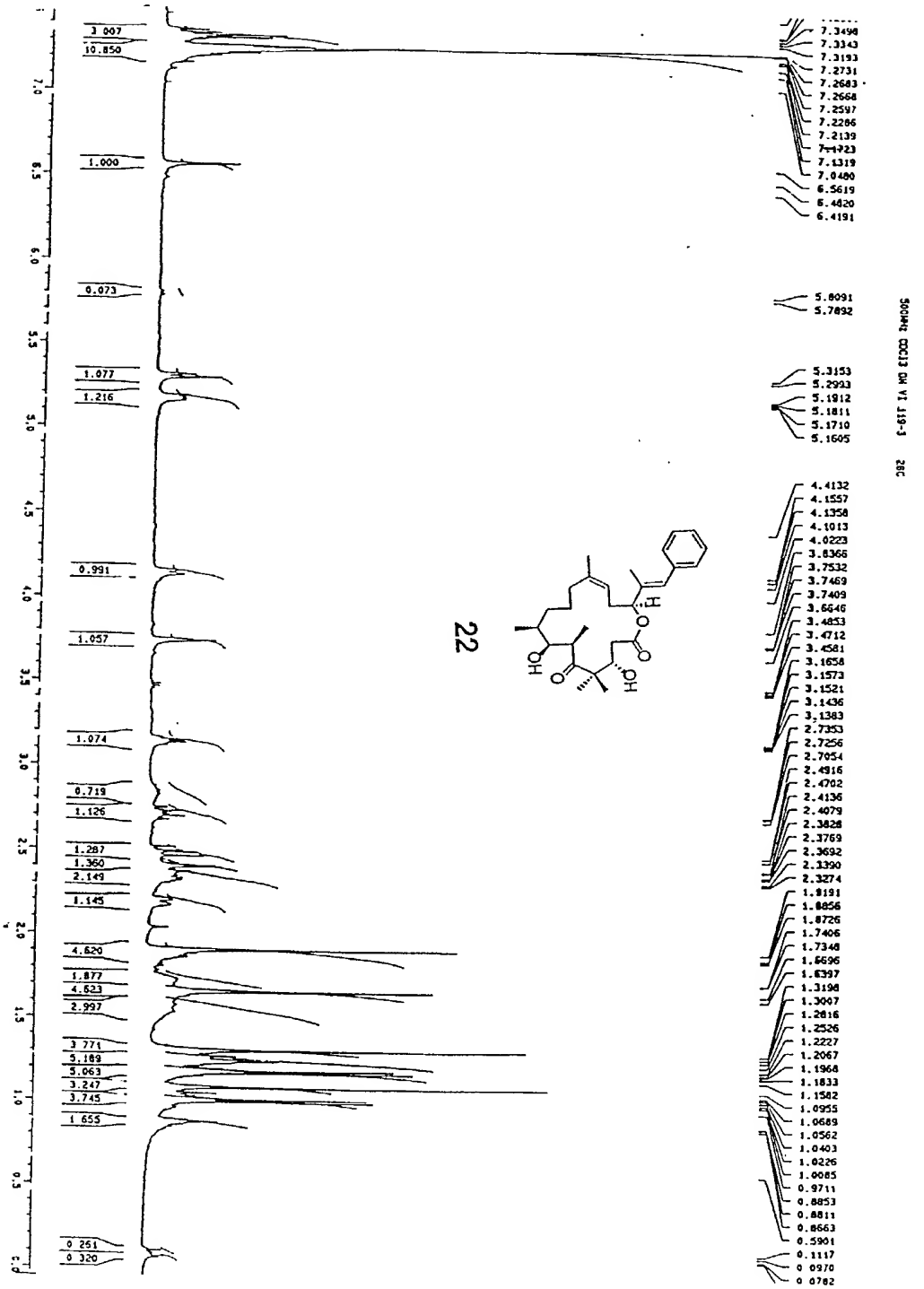


FIGURE 33

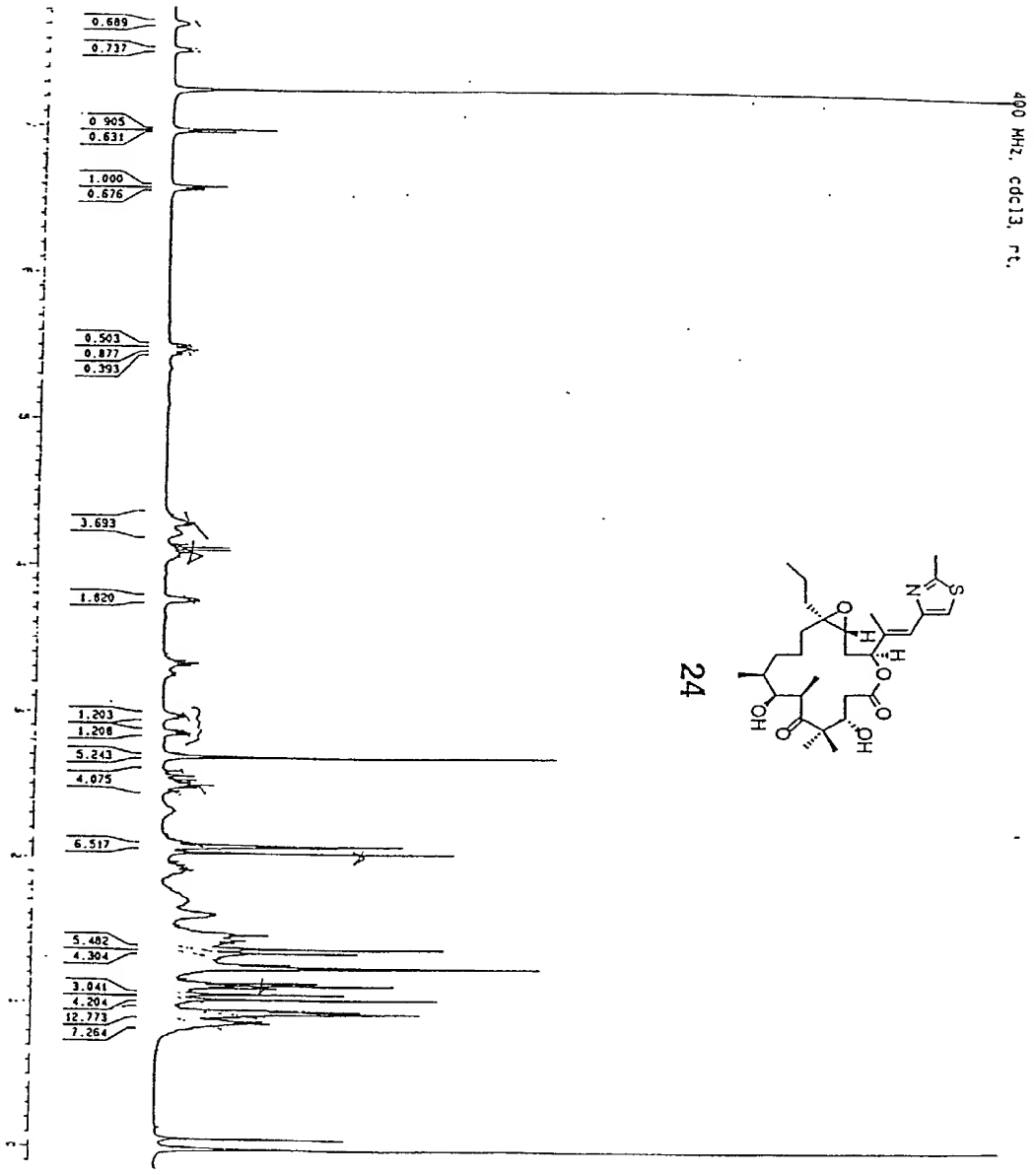

0.689
0.737
0.905
0.631
1.000
0.676
0.503
0.877
0.393
3.693
1.820
1.203
1.208
5.243
4.075
6.517
5.482
4.304
3.041
4.204
12.773
7.264
400 MHz, cdcl3, rt.
24
N
S
O
H
H
O
O
OH
OH

FIGURE 34

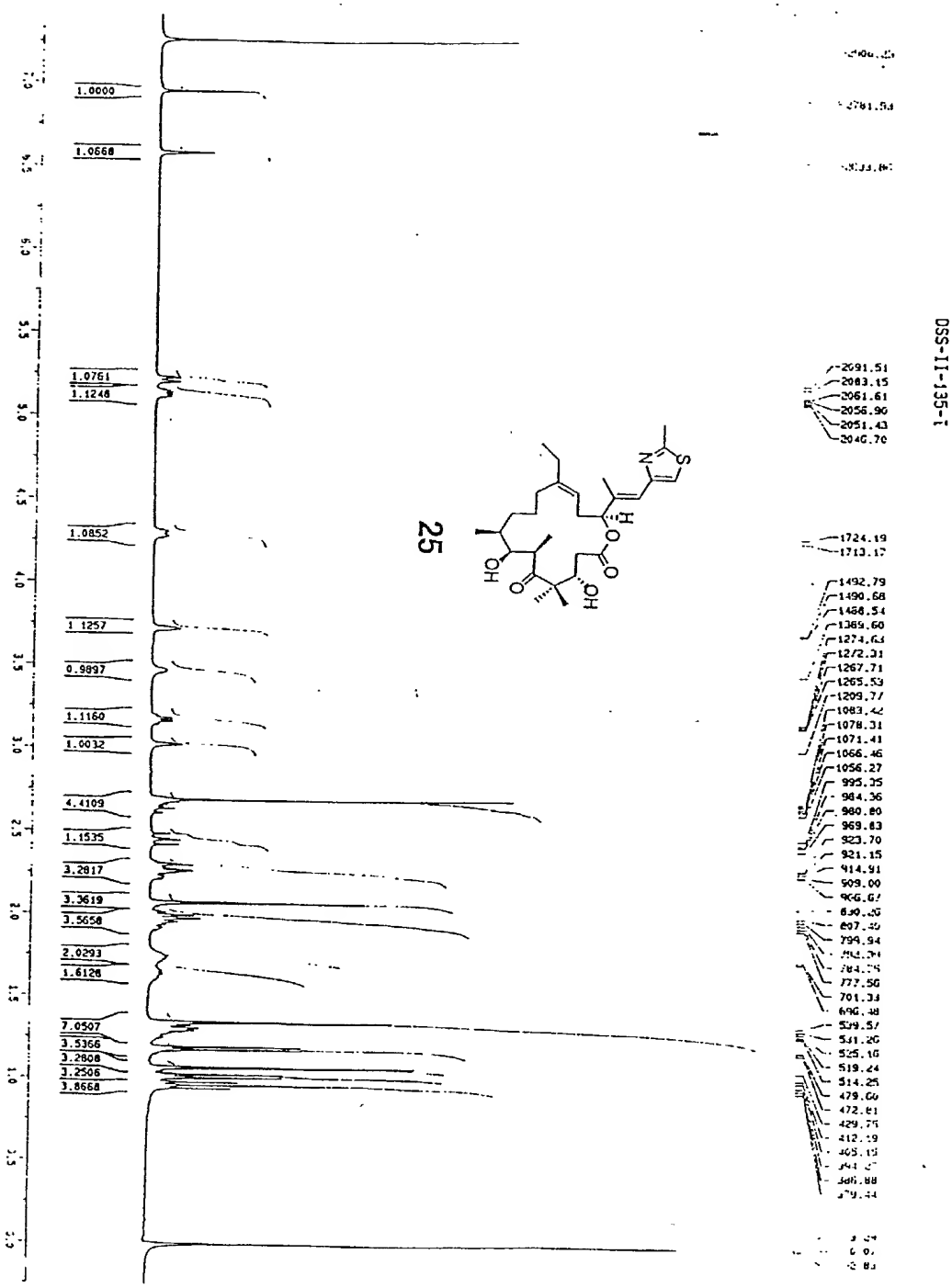

DSS-II-135-1
25
1.0000
1.0668
1.0761
1.1248
1.0852
1.1257
0.9897
1.1160
1.0032
4.4109
1.1535
3.2817
3.3619
3.5658
2.0293
1.6128
7.0507
3.5366
3.2808
3.2506
3.8668

FIGURE 35

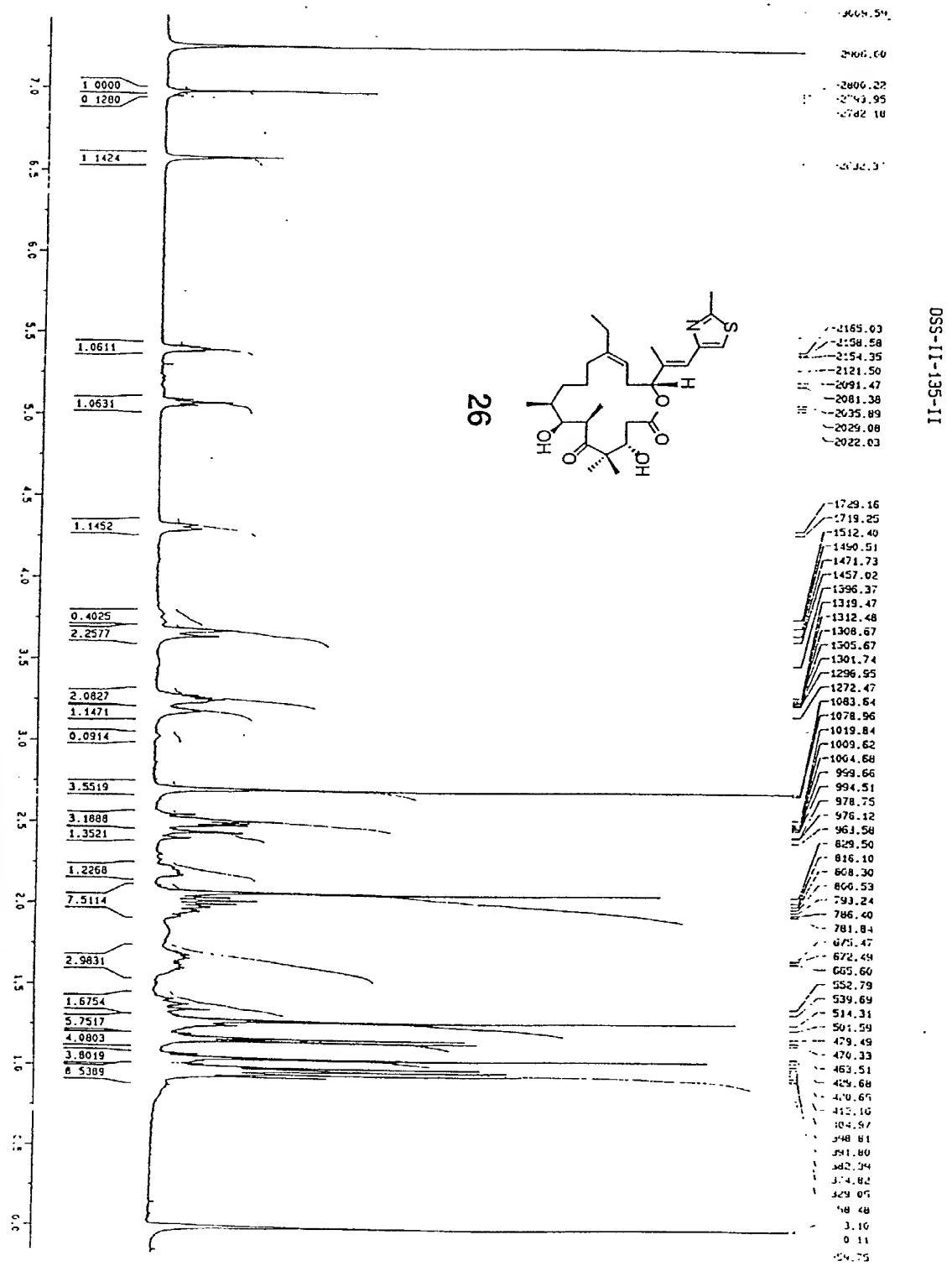


FIGURE 36

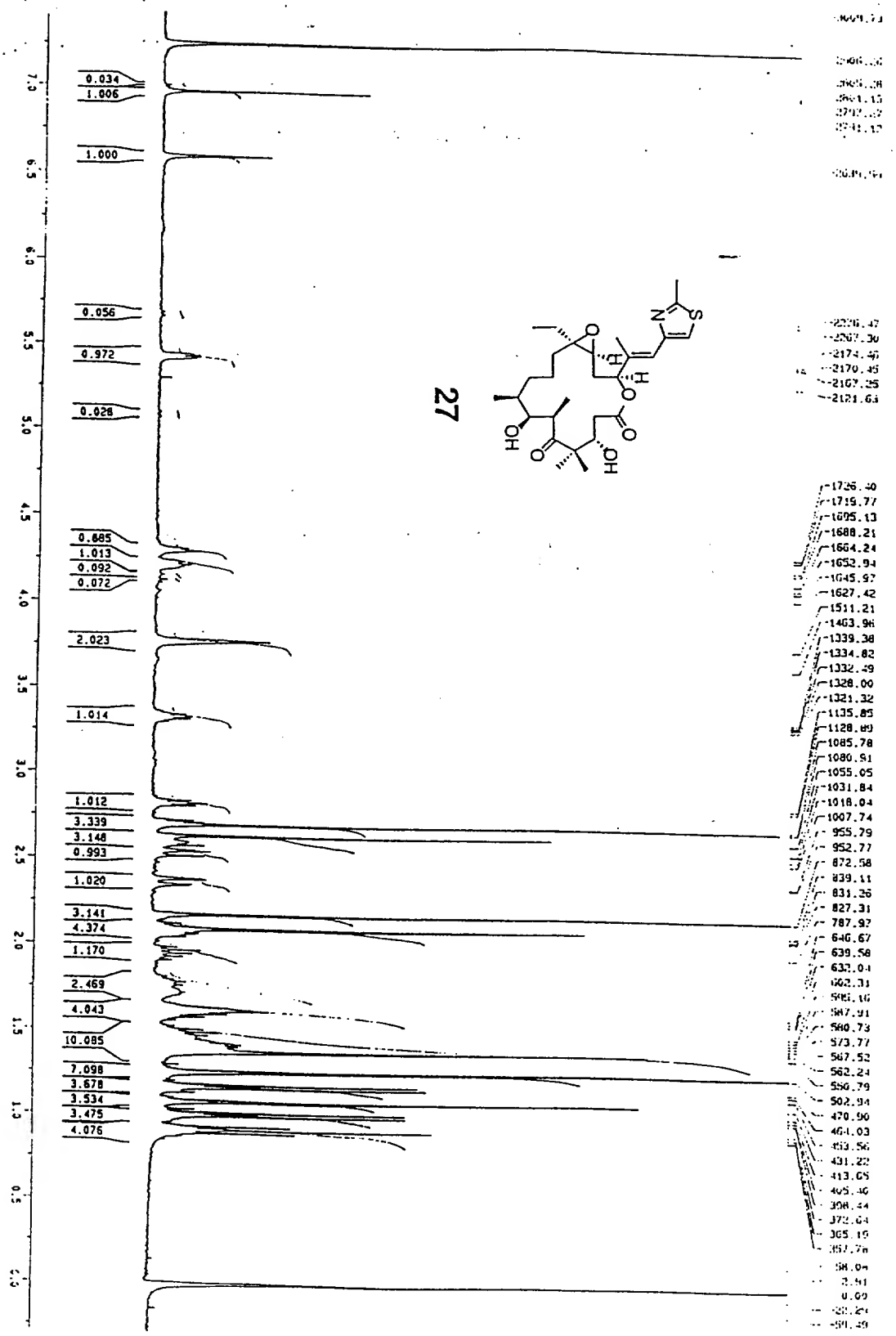


FIGURE 37

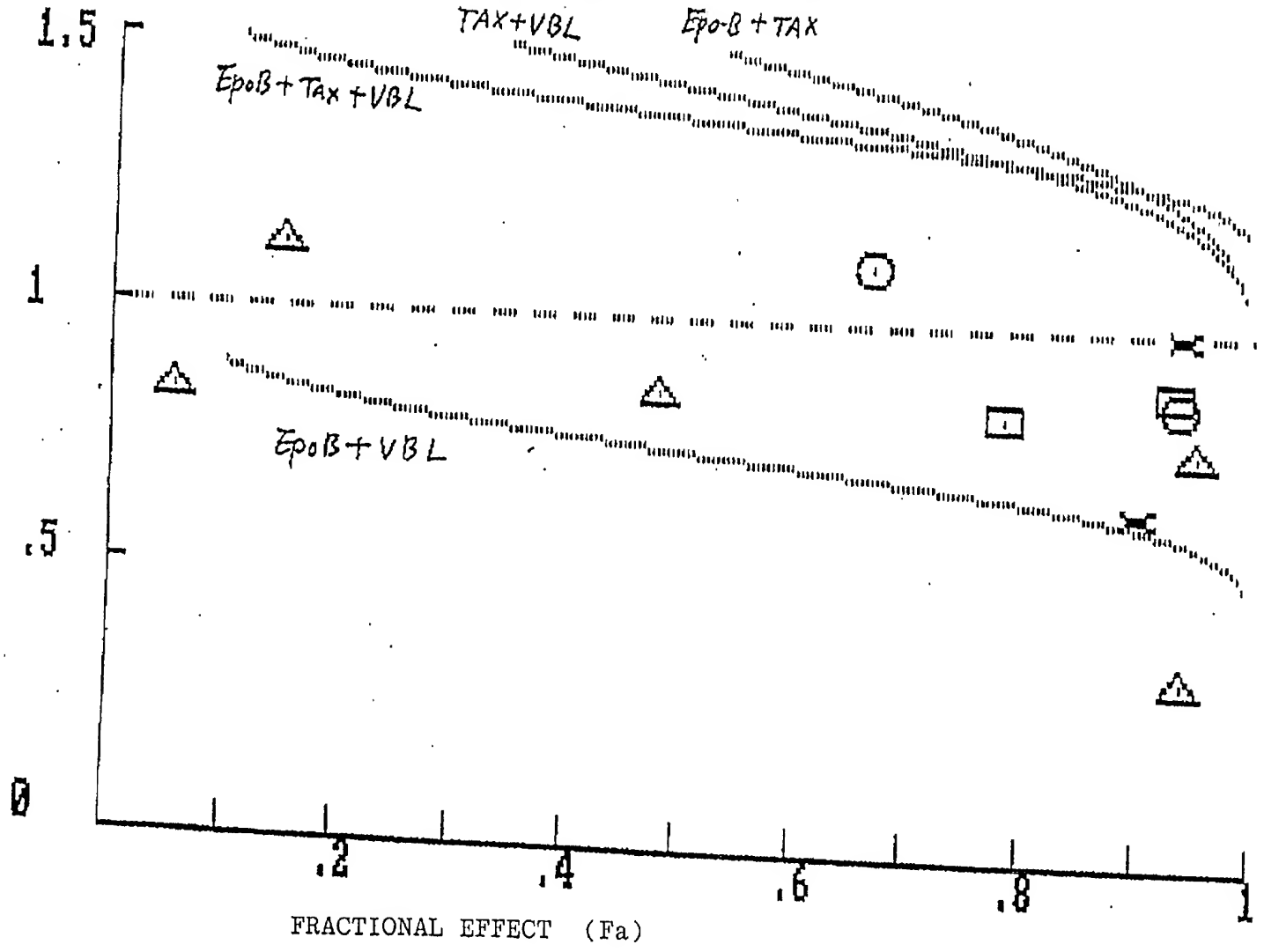
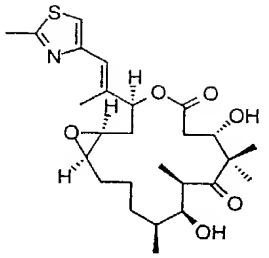
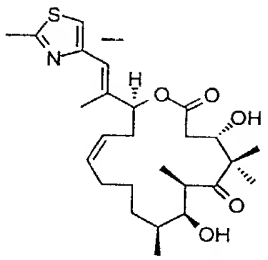

TAX+VBL
Epo-B + TAX
EpoB + Tax + VBL
EpoB + VBL
1.5
1
.5
0
.2
.4
.6
.8
1
COMBINATION INDEX
CI
FRACTIONAL EFFECT (Fa)

Figure 38

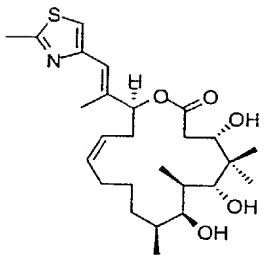


epothilone A
(0.0027)
[0.020]

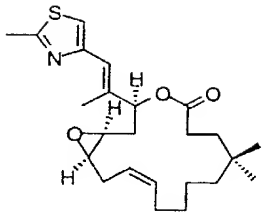


desoxyepothilone A

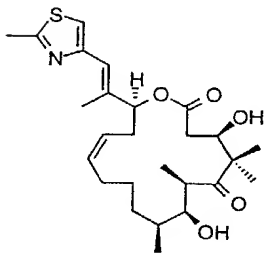
1
(0.022)
[0.012]



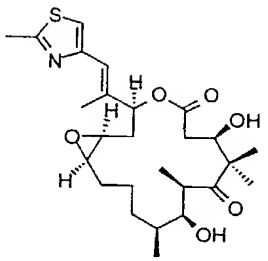
2
(14.23)
[6.28]



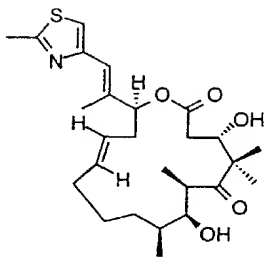
3
(271.1)
[22.4]



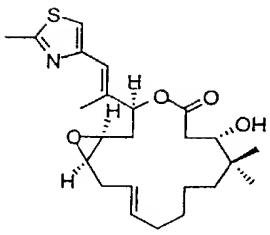
4
(2.12)
[43.0]



5
(>20)
[35.2]

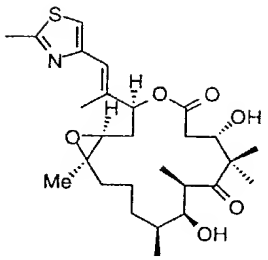


6
(0.052)
[0.035]



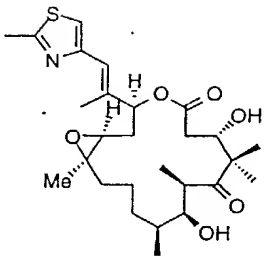
7
(7.36)
[9.82]

Fig. 39



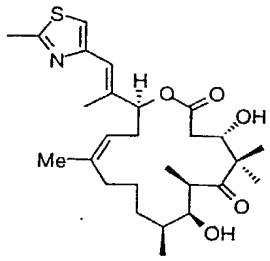
synthetic epothilone B

8
(0.00044)
[0.0026]



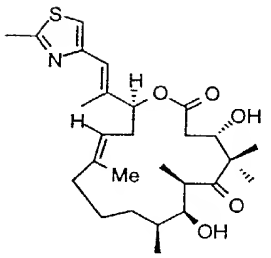
natural epothilone B

9
(0.00017)
[0.0012]

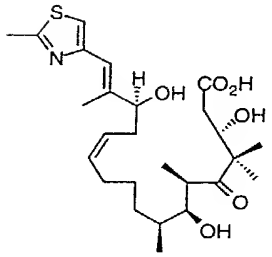


desoxyepothilone B

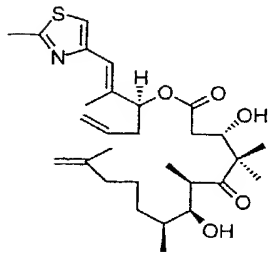
10
(0.0095)
[0.017]



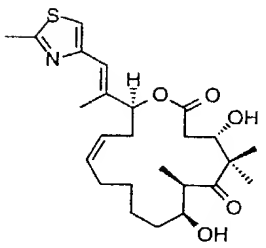
11
(0.090)
[0.262]



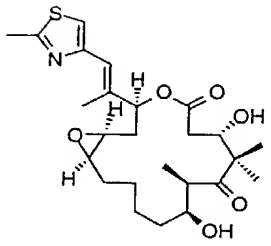
12
(0.79)
[>5]



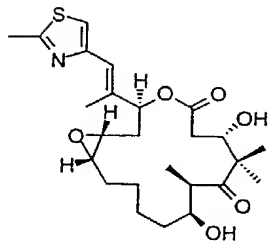
13
(11.53)
[5.63]



14
(5.42)
[5.75]

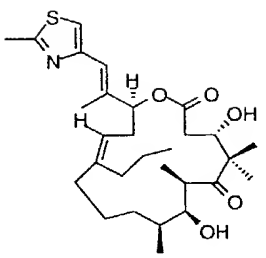


15
(0.96)
[5.95]

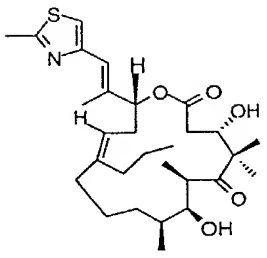


16
(7.47)
[16.48]

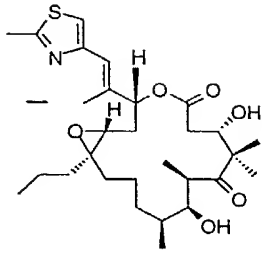
Fig. 40



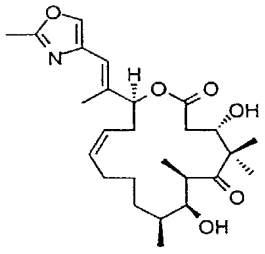
17
(0.090)
[0.254]



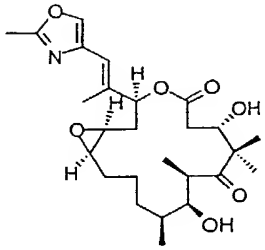
18
(1158)
[>720]



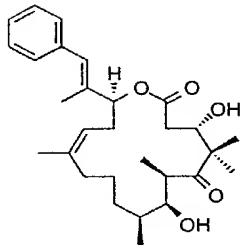
19
(0.96)
[>1.0]



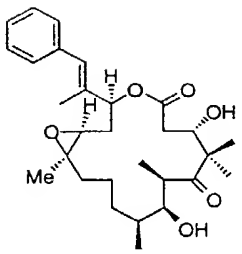
20
(0.030)
[0.049]



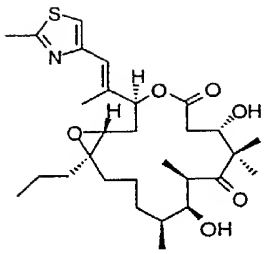
21



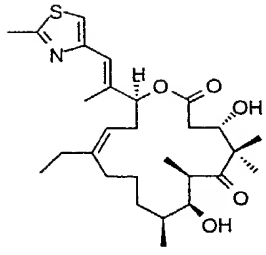
22
(0.098)
[0.146]



23

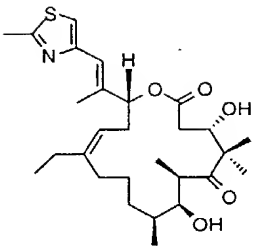


24
(0.0043)
[0.032]

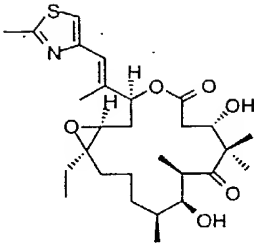


25
(0.021)
[0.077]

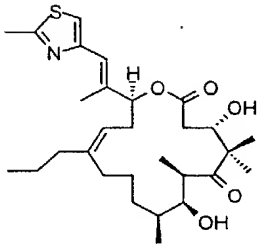
Fig. 41



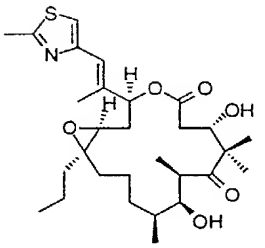
26
(0.055)
[0.197]



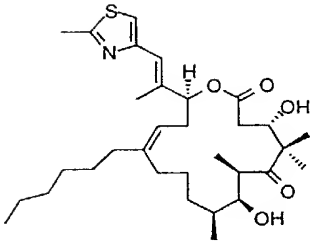
27
(0.0010)
[0.0072]



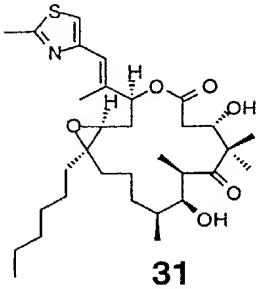
28
(0.039)
[0.067]



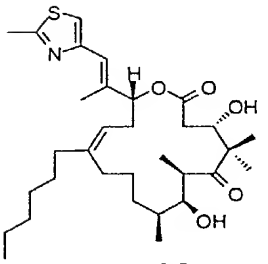
29
(0.0038)
[0.0064]



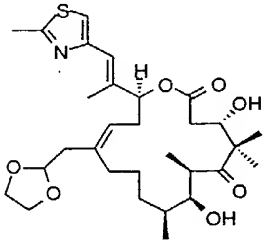
30
(0.044)
[0.108]



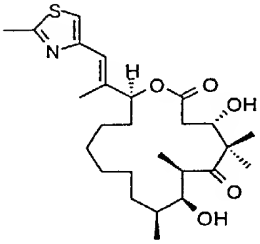
31
(0.027)
[0.049]



32
(0.063)
[0.380]

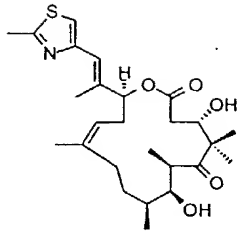


33
(0.0031)
[0.0093]

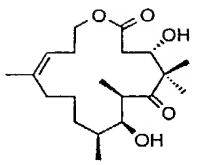


34
(0.143)
[0.276]

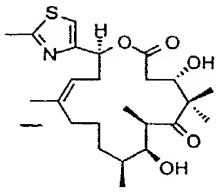
Fig. 42(A)



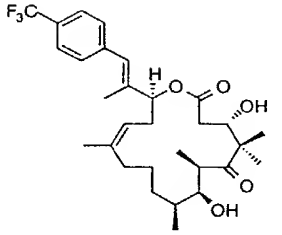
35
(>10)
[8.95]



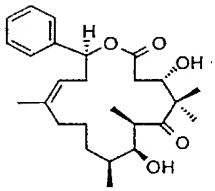
36
(234.5)
[>10]



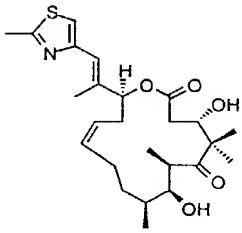
37
(3.25)
[1.20]



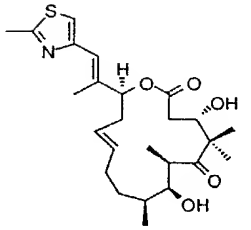
38
(0.254)
[>5.0]



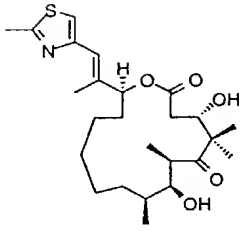
39
(1.80)
[>5.0]



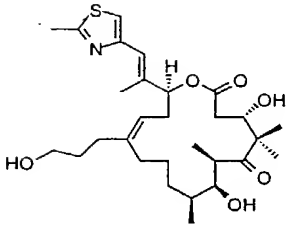
40
(36.9)
[47.3]



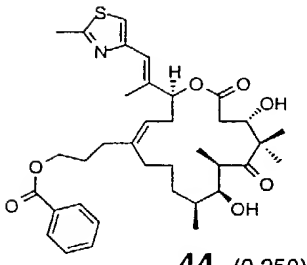
41
(60.1)
[59.2]



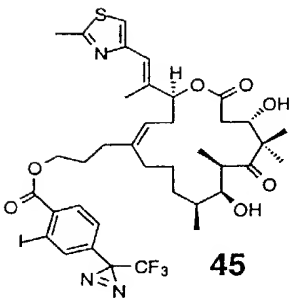
42
(7.41)
[12.9]



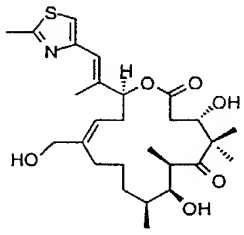
43
(0.0095)
[0.167]



44 (0.250)
[0.905]

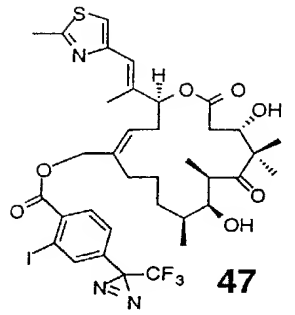


45

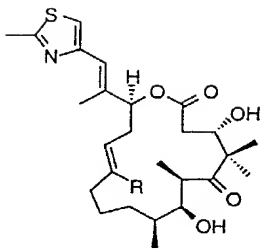


46 (0.049)
[>1.0]

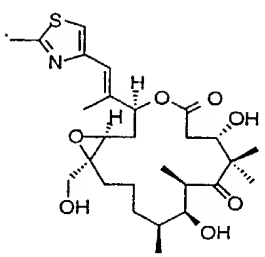
Fig. 42(B)



47



48 R = $(CH_2)_3OH$



49

Fig. 42(C)

Fig. 43(A)

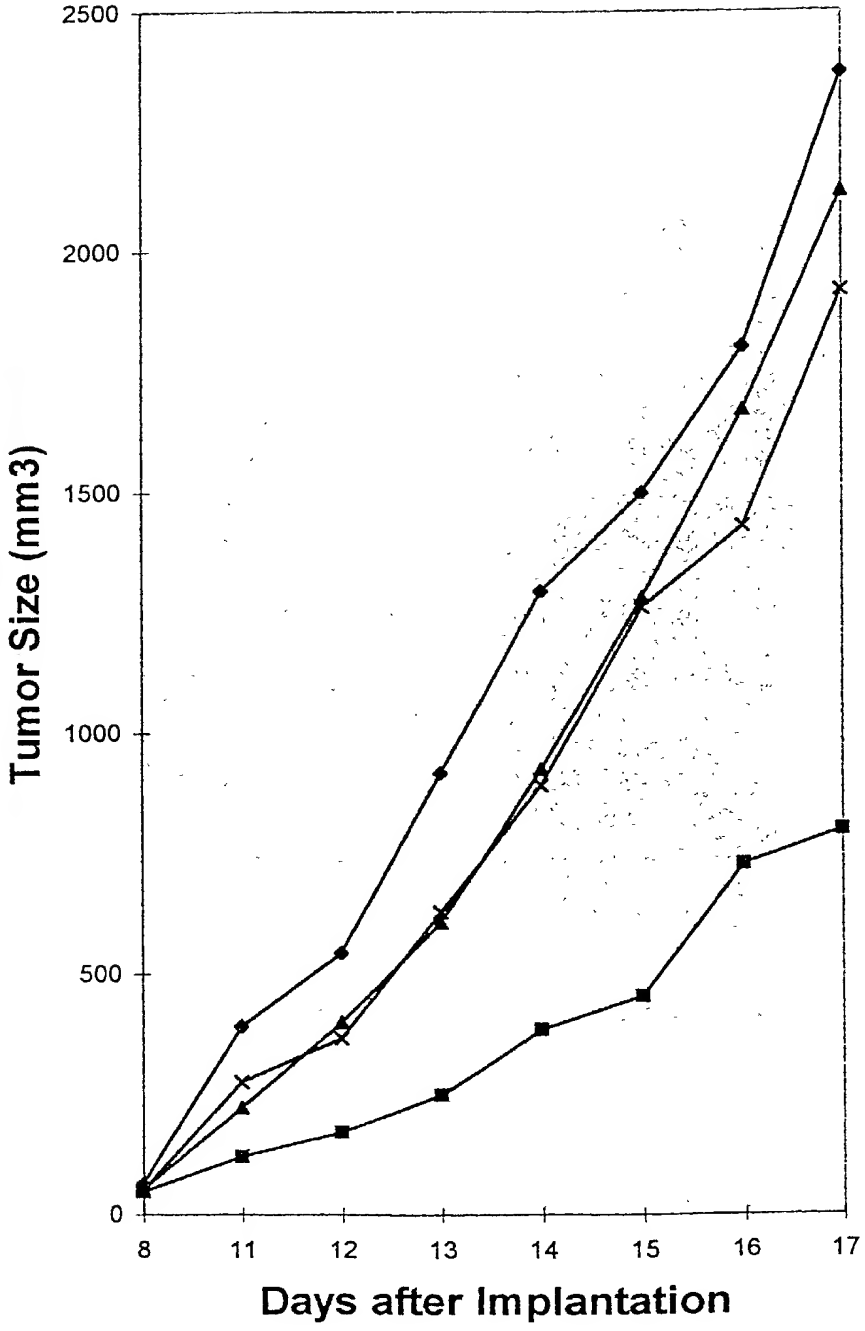
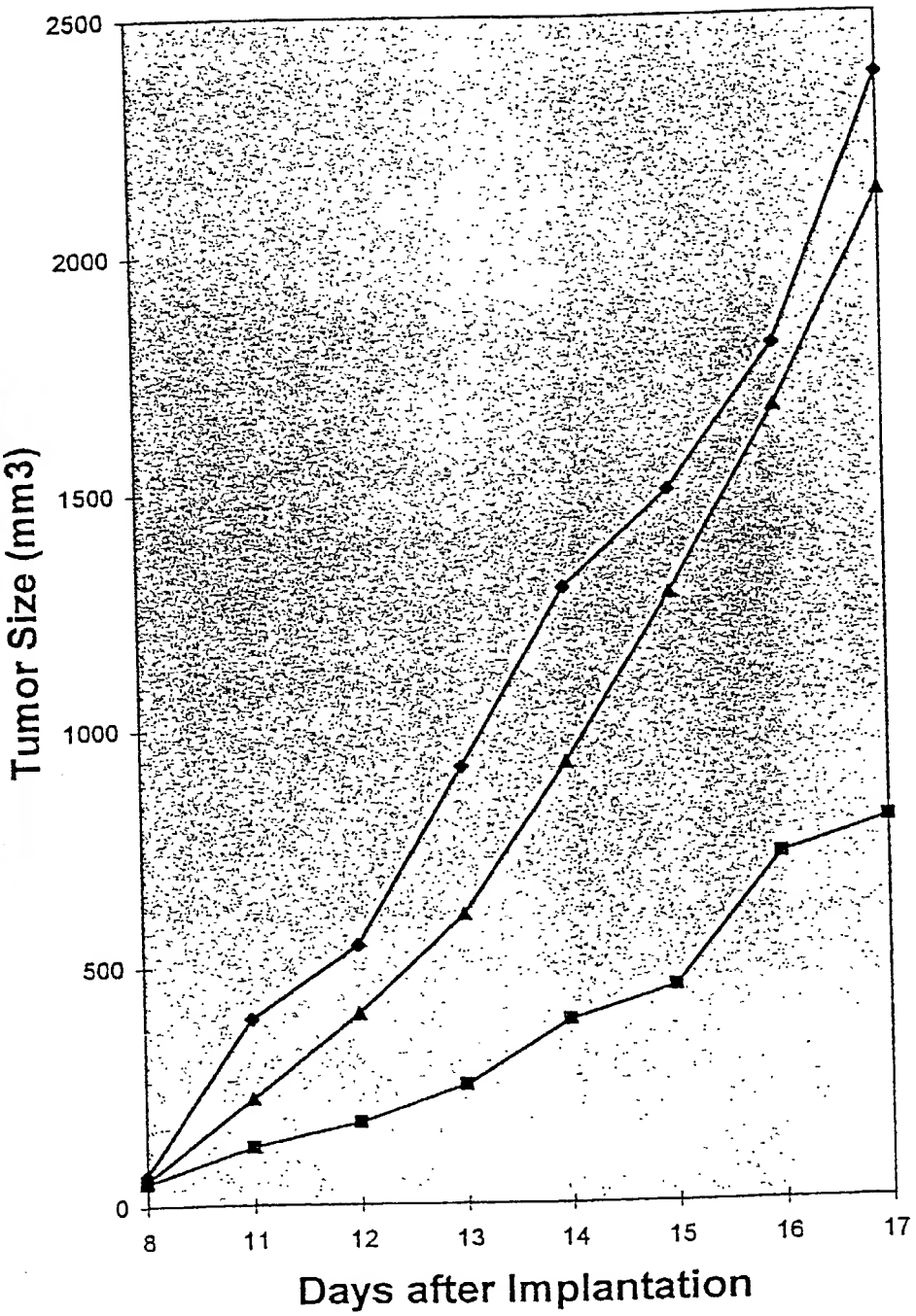

2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation

Fig. 43(B)


2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation

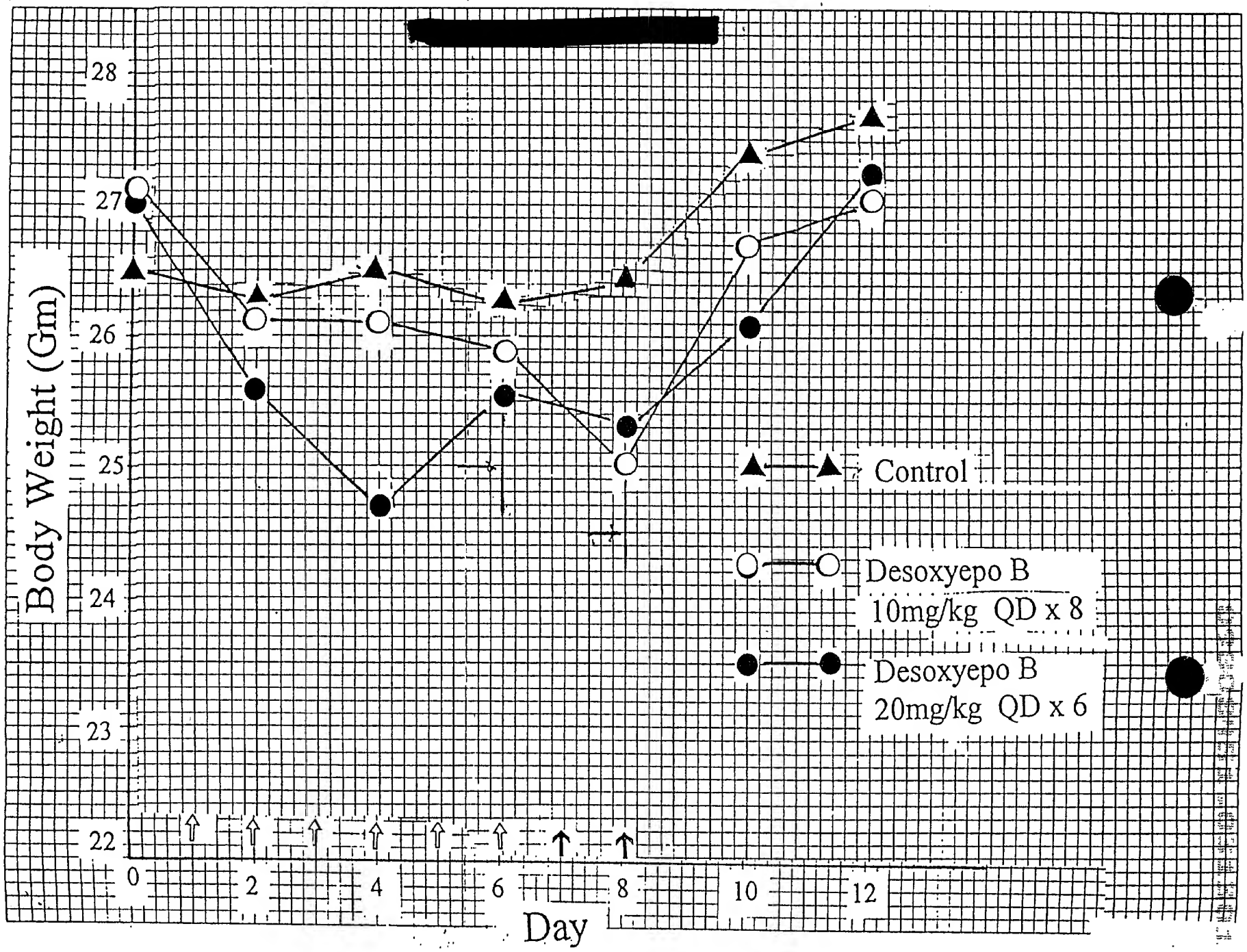

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
Day
Control
Desoxyepo B
10mg/kg QD x 8
Desoxyepo B
20mg/kg QD x 6

Fig. 44(A)

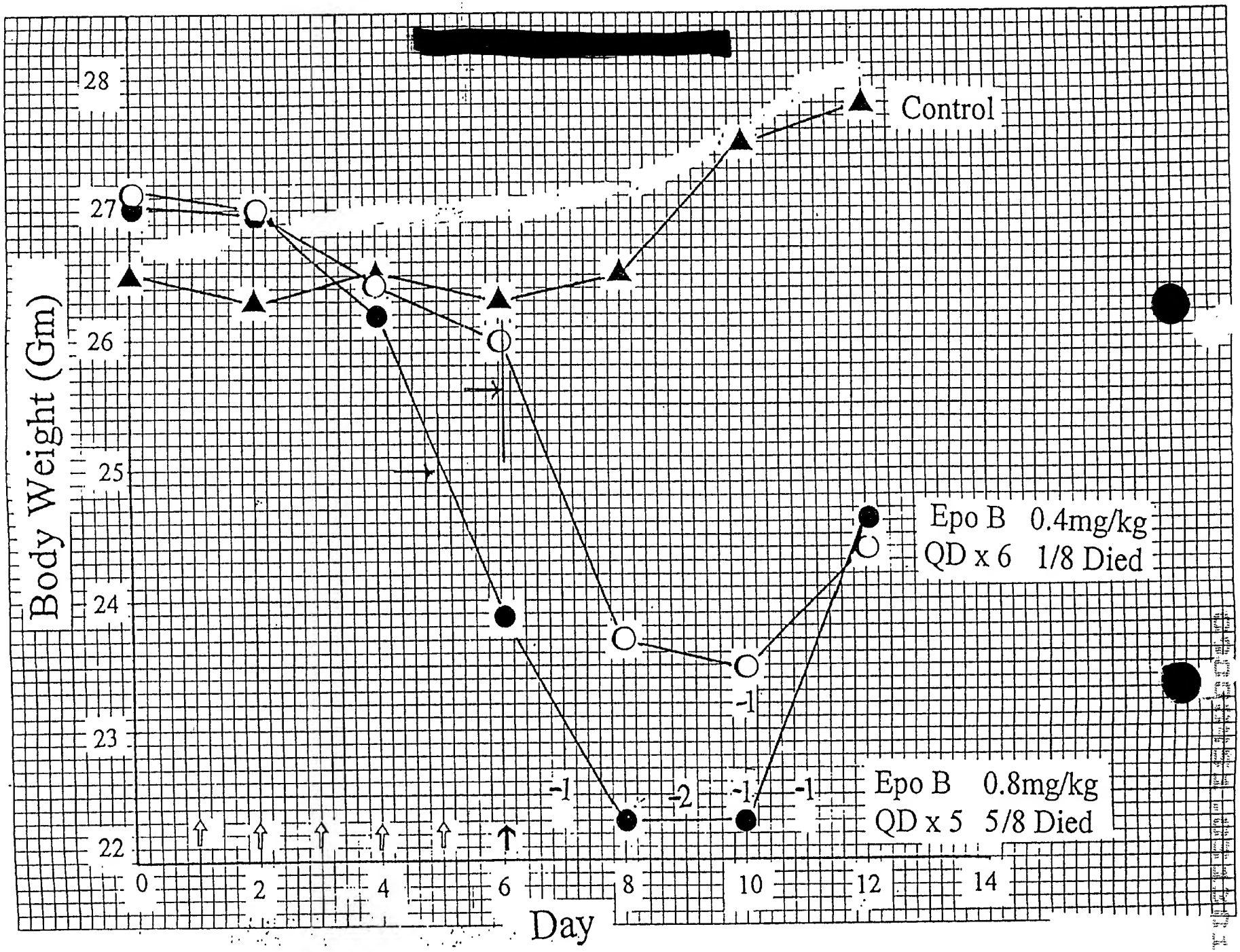

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
14
Day
Control
Epo B 0.4mg/kg
QD x 6 1/8 Died
Epo B 0.8mg/kg
QD x 5 5/8 Died
-1
-1
-2
-1
-1

Fig. 44(B)

Fig. 45(A)

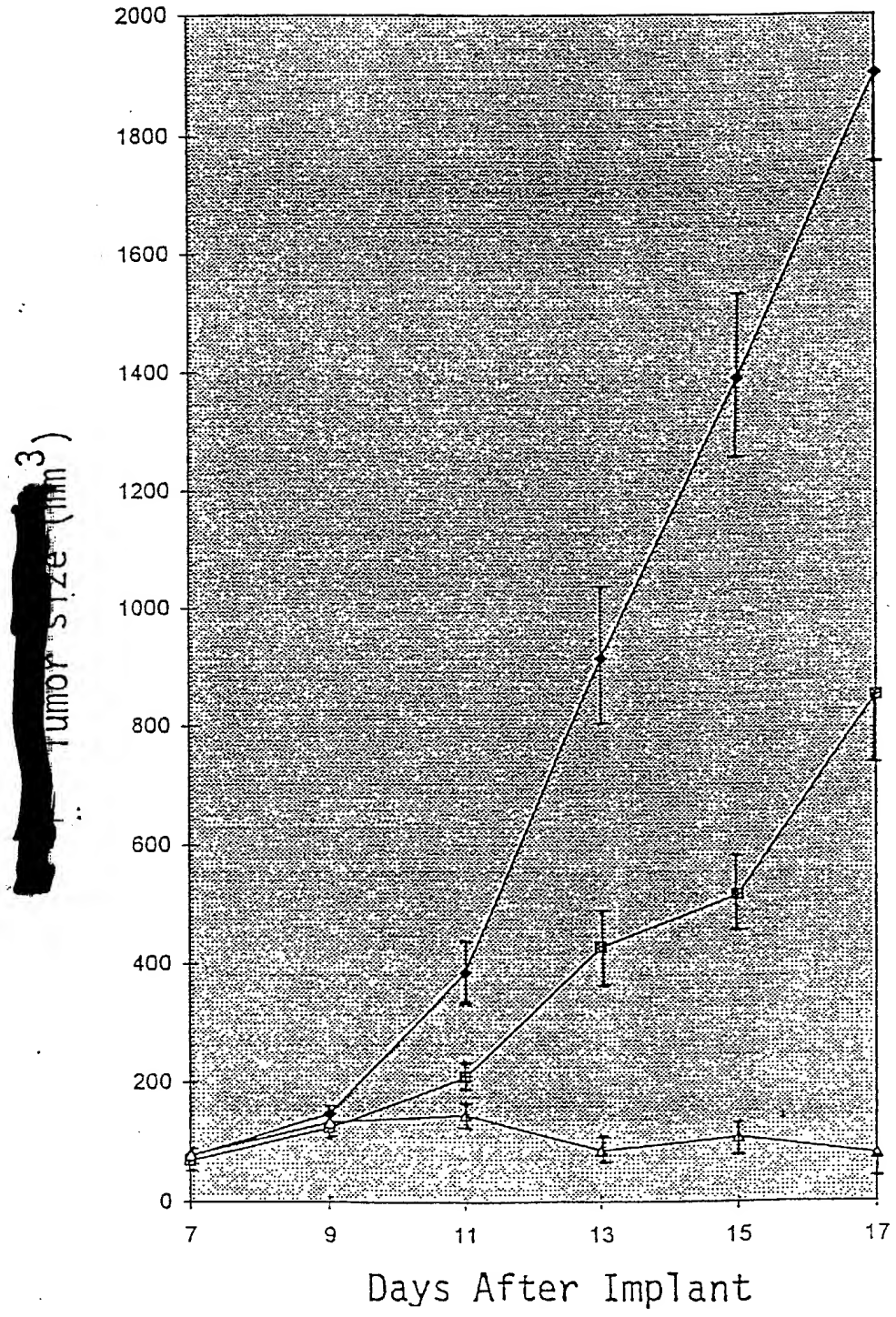
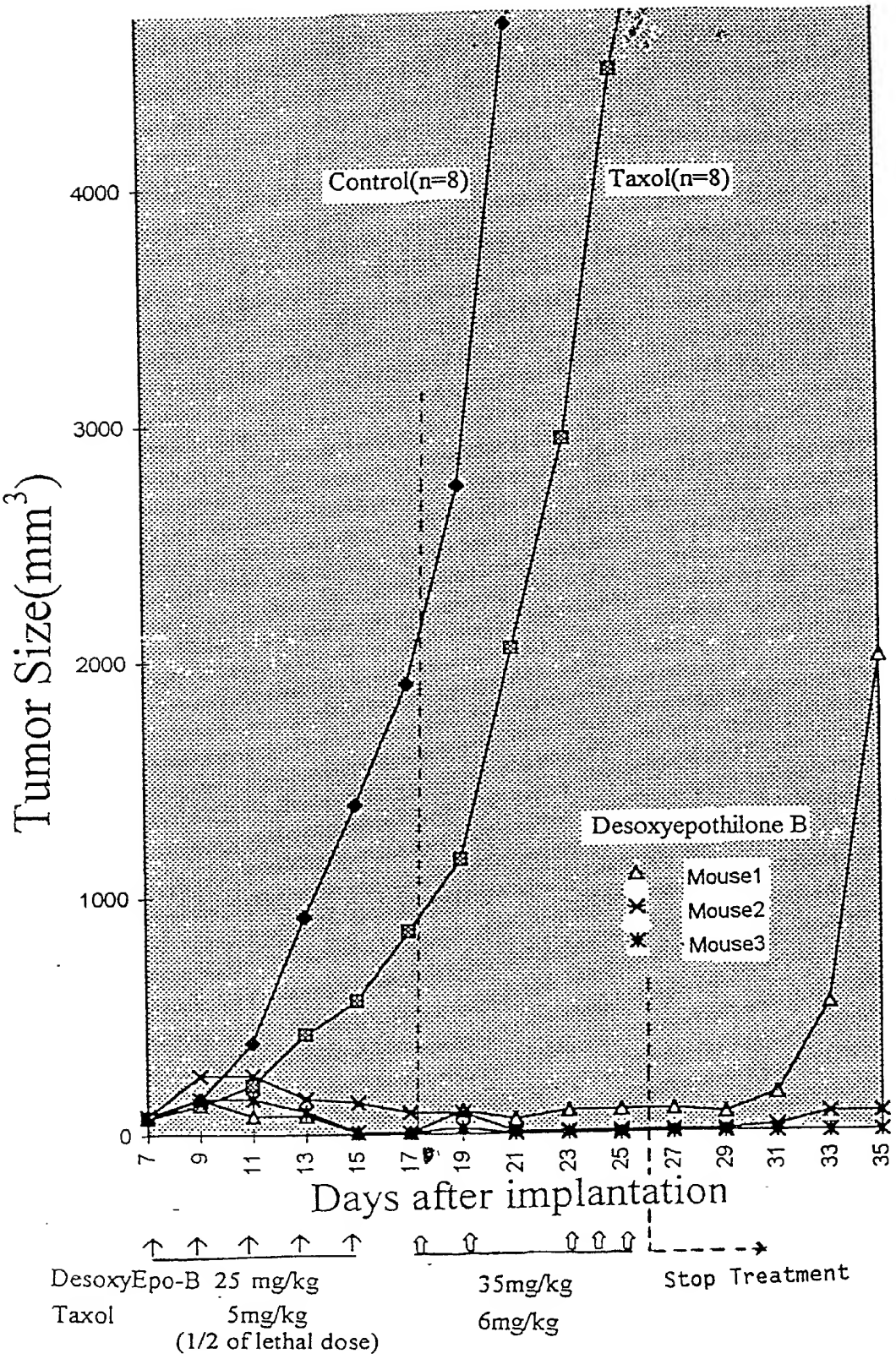

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Tumor size (mm3)
7
9
11
13
15
17
Days After Implant

Fig. 45(B)


Control(n=8)
Taxol(n=8)
Desoxyepothilone B
Mouse1
Mouse2
Mouse3
Tumor Size(mm3)
4000
3000
2000
1000
0
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
Days after implantation
DesoxyEpo-B 25 mg/kg
Taxol 5mg/kg
(1/2 of lethal dose)
35mg/kg
6mg/kg
Stop Treatment

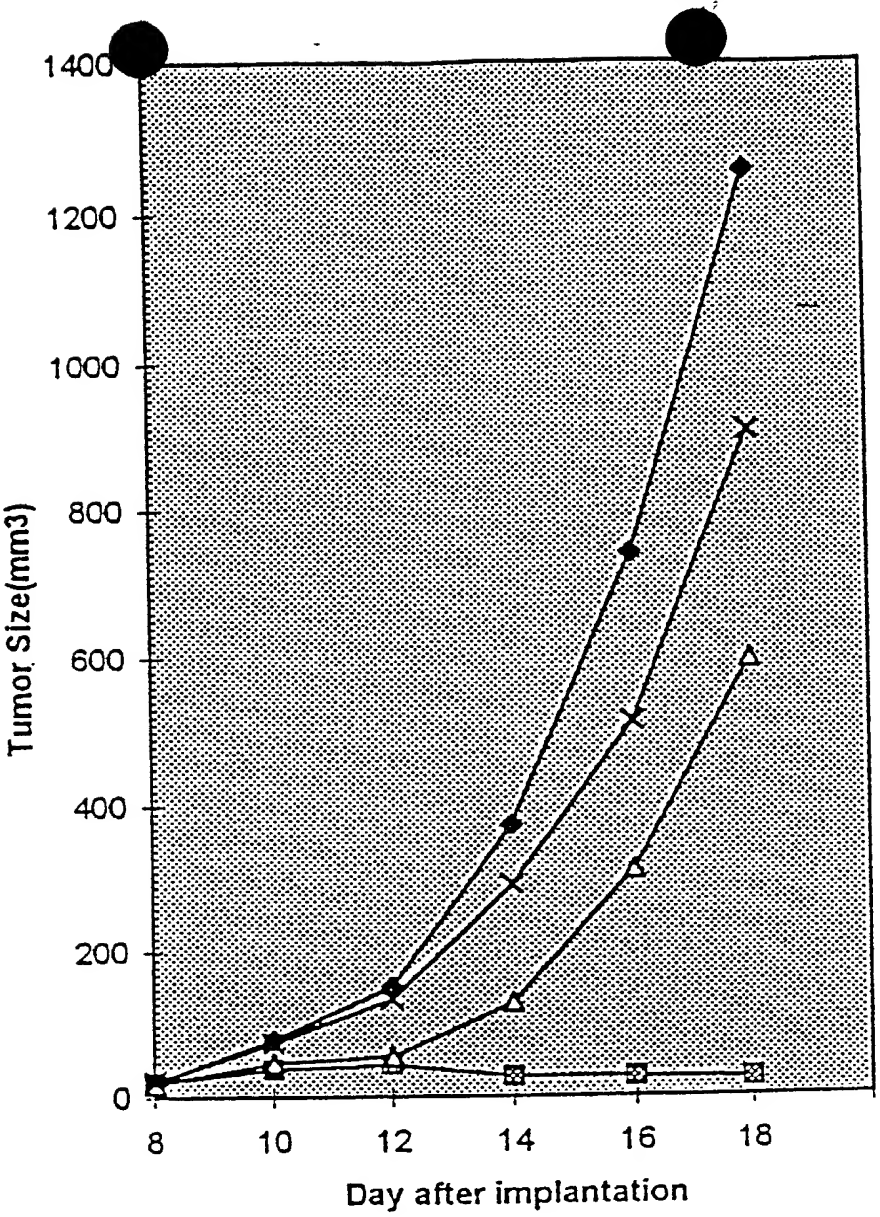
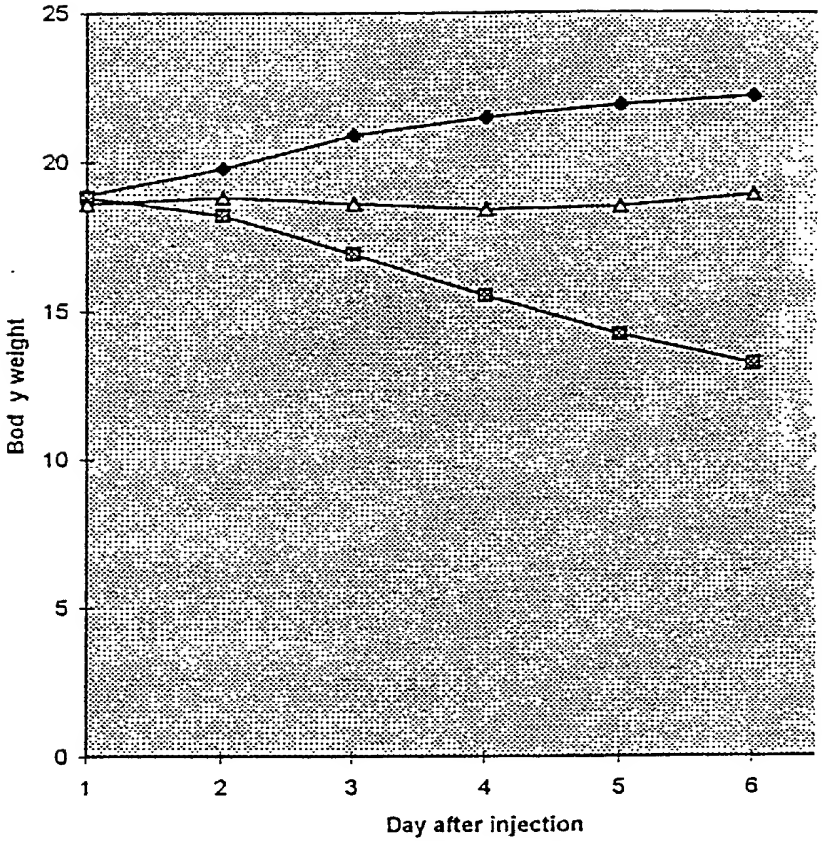

1400
1200
1000
800
600
400
200
0
Tumor Size(mm3)
8
10
12
14
16
18
Day after implantation

Fig. 46

Fig. 47



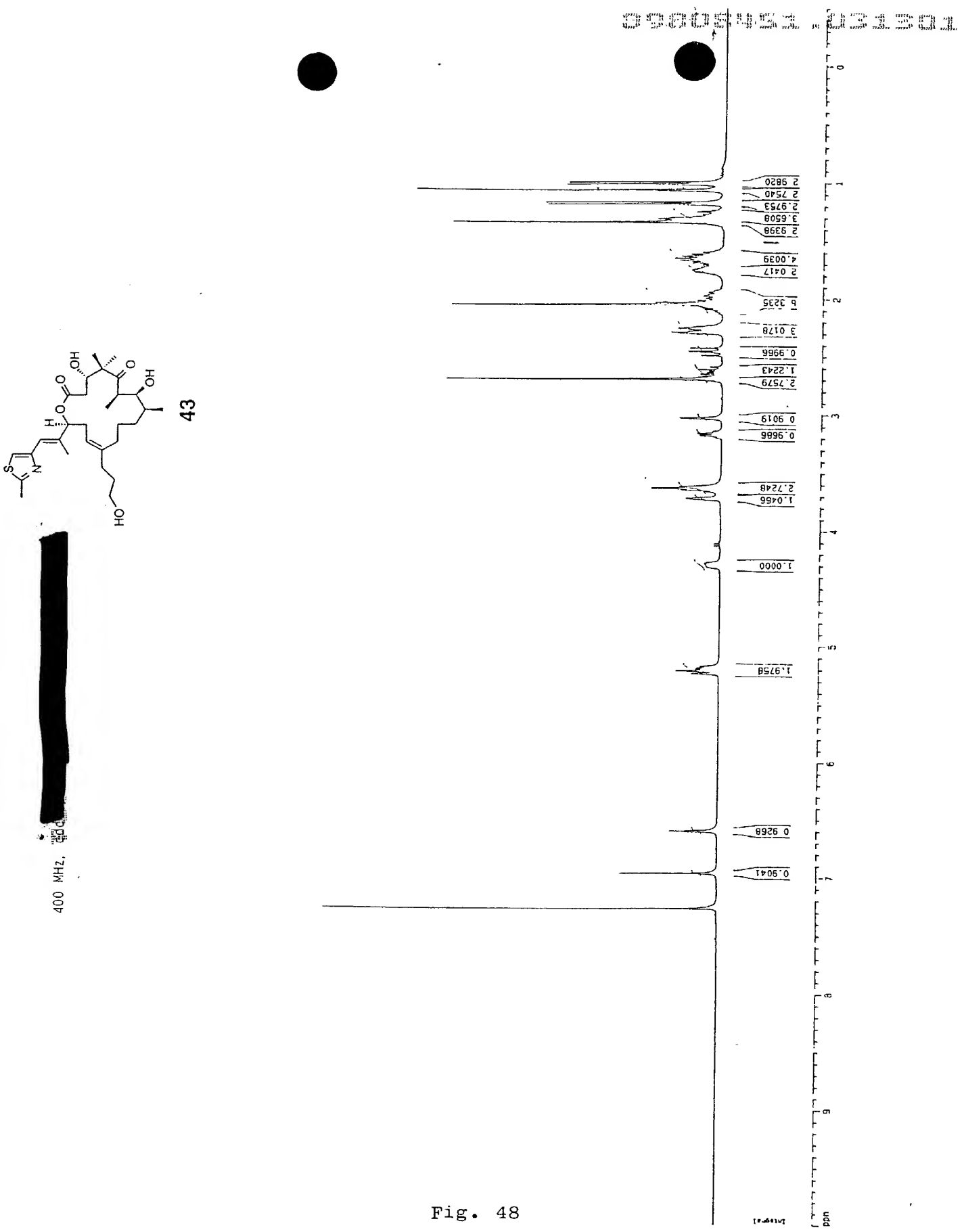

43
400 MHz, [redacted]
2.9820
2.7540
2.9753
3.6508
2.9398
4.0039
2.0417
6.3235
3.0178
0.9966
1.2243
2.7579
0.9019
0.9686
2.7248
1.0466
1.0000
1.9758
0.9268
0.9041
ppm

Fig. 48

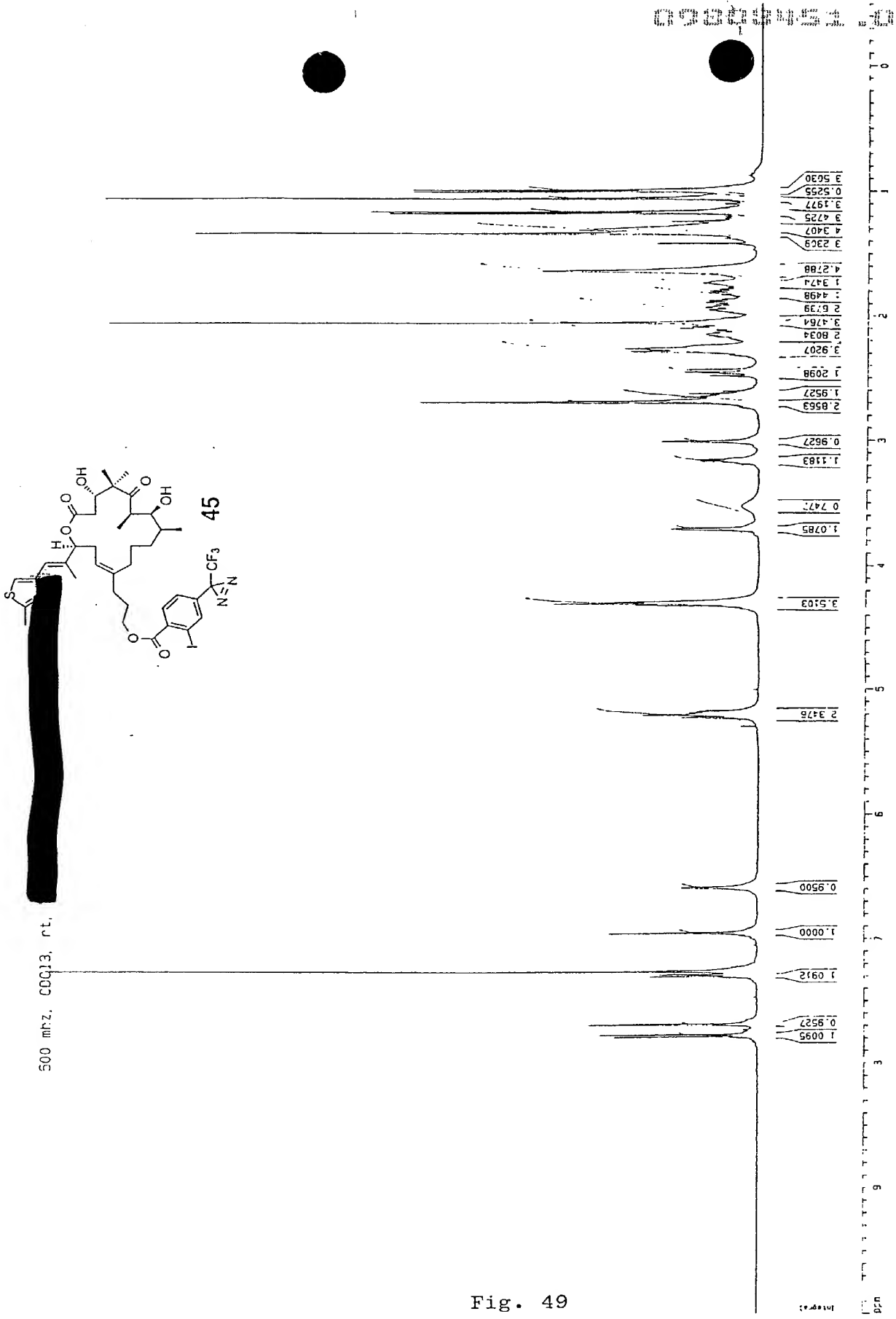


Fig. 49

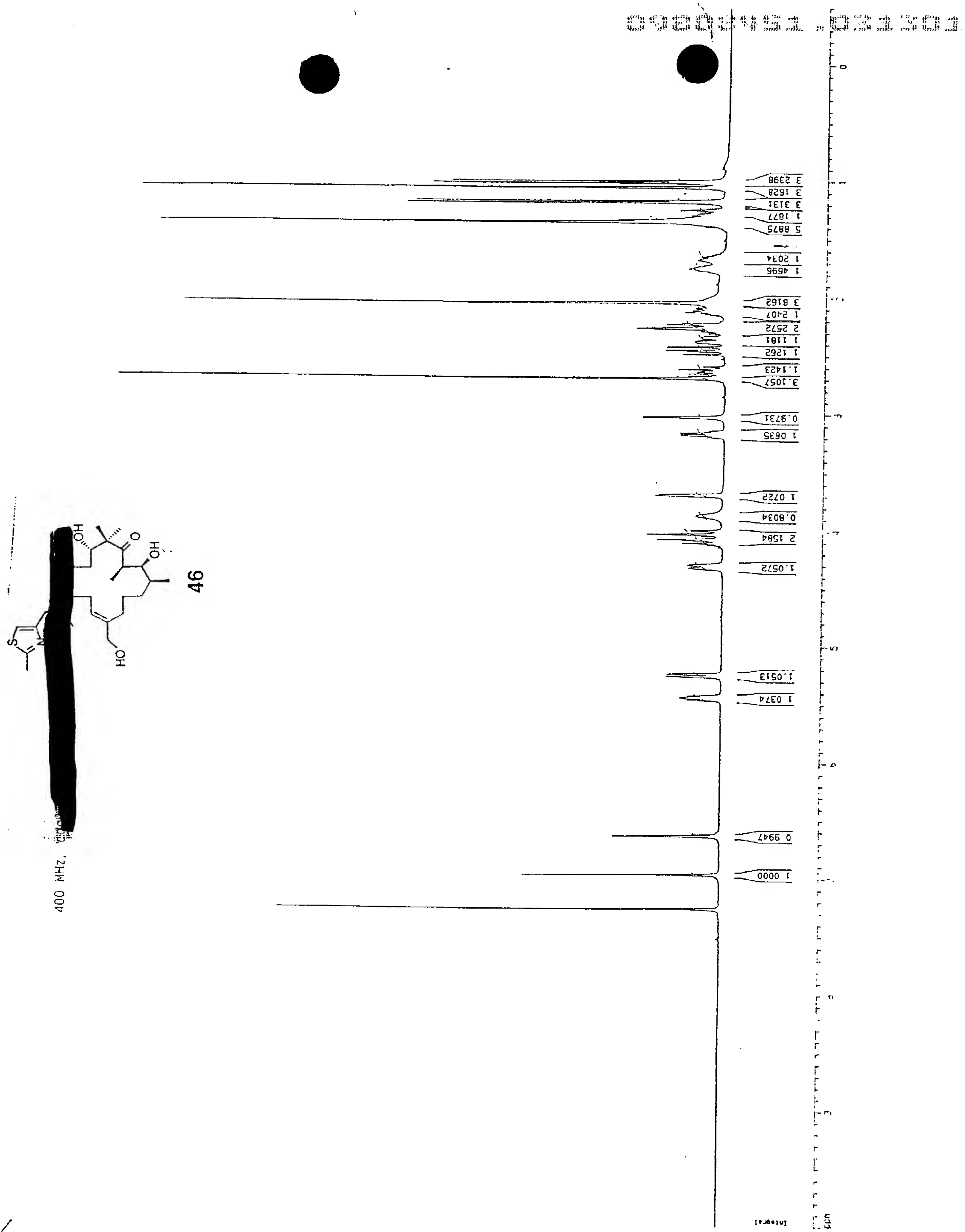


Fig. 50

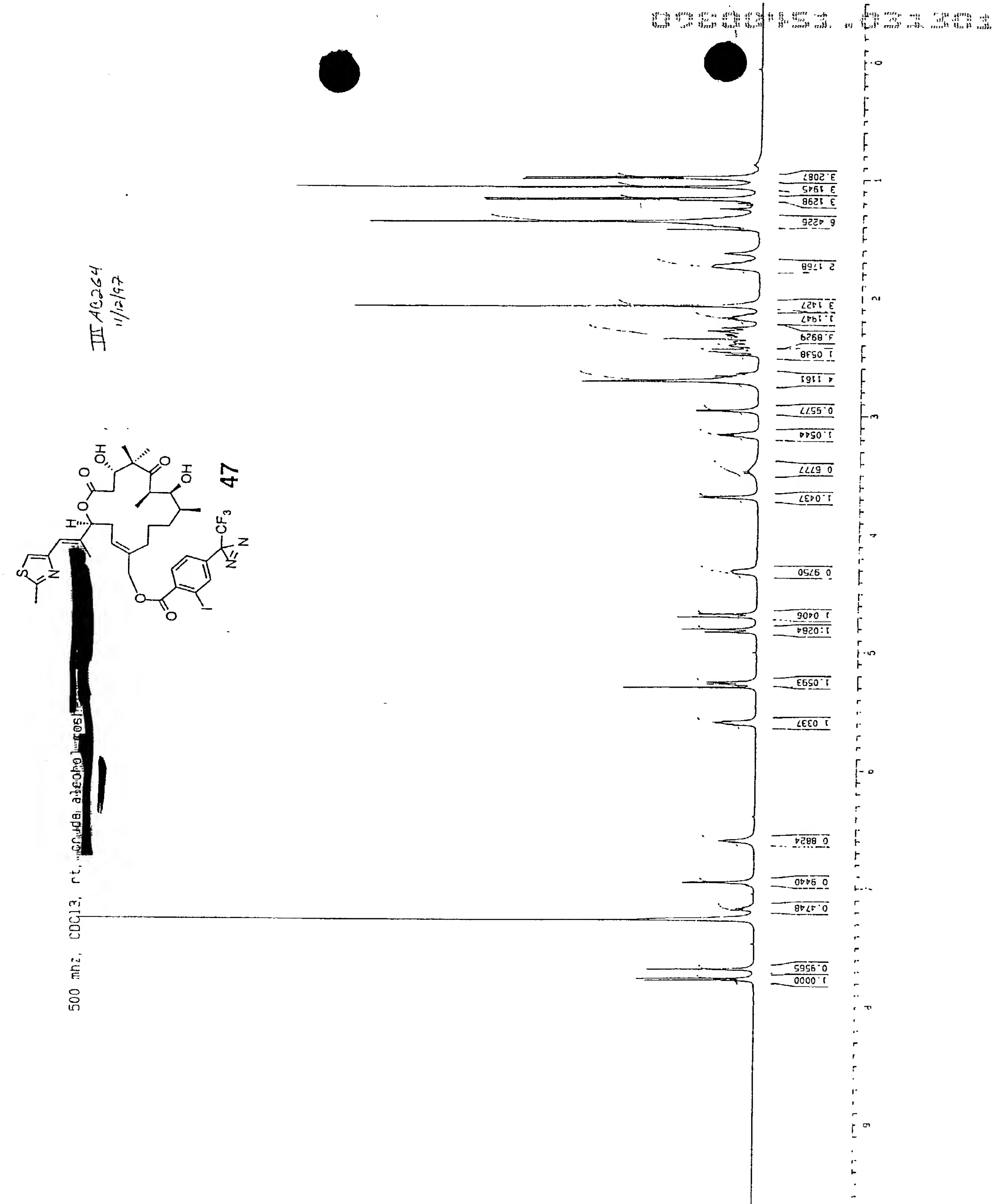


Fig. 51

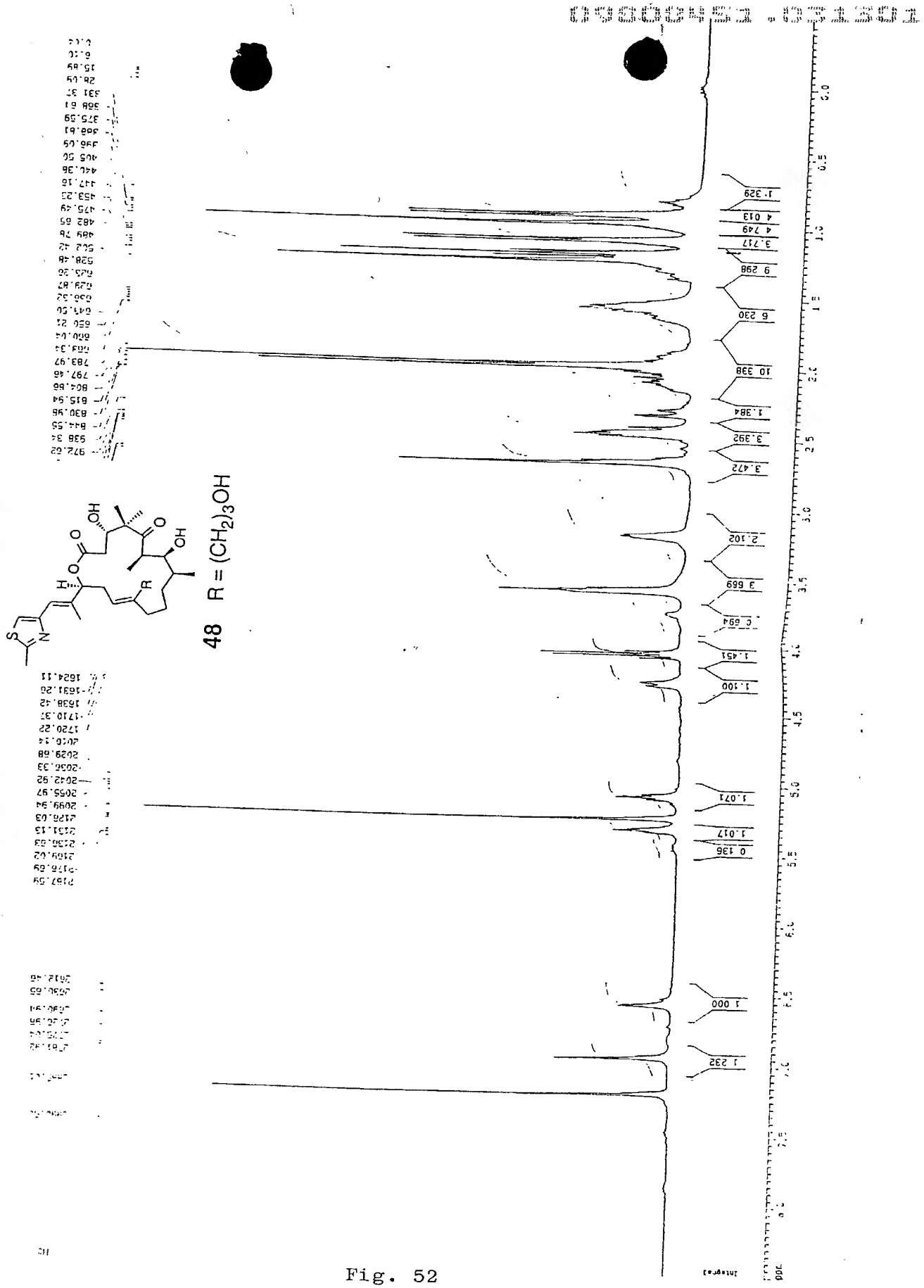


Fig. 52